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العلاقة بين المؤكسدات ومضادات الاكسدة مع السايتوكين وهرمون المحفز الجريبي في النساء المصابات في السمنه مع داء السكري

اطروحة

مقدمه إلى مجلس كلية العلوم – جامعة بابل

وهي جزء من متطلبات نيل درجة

الدكتوراه فلسفة في علوم الكيمياء (كيمياء حياتية)

من قبل

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الخلاصة

الخلفية العلمية: يمثل داء السكري من النوع الثاني حوالي 90٪ من جميع حالات مرض السكري النوع الثاني ، تقل الاستجابة للأنسولين ، وهذا ما يعرف بمقاومة الأنسولين ، يكون الأنسولين غير فعال ويتم السيطره علية في البداية من خلال زيادة إنتاج الأنسولين للحفاظ على توازن الكلوكوز ، ولكن بمرور الوقت ، يتناقص إنتاج الأنسولين ، مما يؤدي إلى مرض السكري النوع الثاني .

أصبحت السمنة الآن شائعة جدًا بين سكان العالم لدرجة أنها بدأت في استبدال نقص التغذية والأمراض المعدية حيث تعتبر عامل مساهم في تدهور الصحة ناتج عن مزيج من الإفراط في تناول التغذية ونقص النشاط البدني والعامل الوراثي. السبب الرئيسي للسكري نوع الثاني هو العامل الوراثي أو شكاوى الغدد الصماء أو الأدوية أو الاضطرابات النفسية. في العراق ، يتزايد حدوث مرض سكري نوع ثاني في الأشخاص الذين يعانون من السمنة ويظهر عبئًا كبيرًا على الصحة العامة والنمو الاجتماعي والاقتصادي.

الأهداف: تهدف الدراسة الحالية إلى قياس بعض السيتوكينات المتعلقة بالسمنة بما في ذلك بروتين احادي الخليه ومستقبل الاديبونكتين ADIPOR1 والاديبونكتين ADIPO في الأفراد الاصحاء والأفراد المصابين بالسمنة المفرطة والسكري ومرضى السكري غير البدينين. تطرقت الدراسة للقياس مستويات مصل مالونديلدهايد malondialdehyde (MDA) ، مضادات الأكسدة الكليه (TAC) وحالة الأكسدة الكلية (TOS) ولمعرفة العلاقة المحتملة بين هذه العوامل والمعايير الأخرى المقدرة أيضًا مثل ؛ مؤشر كتلة الجسم ، مستو السكر الصائم FBS ، واكسده الدهون.

الطريقة العمل: يتكون تصميم دراسة الحالة من 30 مريضًا مصابًا بالسمنة المفرطة و 30 مريضًا مصابًا بمرض السكري غير البدينين ، و 15 مريضًا بمراقبة السمنة و 15 مريض غير مصاب بالسمنة من الاصحاء. المجموعات الأربع غير متطابقة مع العمر. يتم تحديد مستوى السكر الصائم في الدم FSG، malondialdehyde (MDA) ، ملف الدهون ، TAC و TOS عن طريق طريقة القياس اللوني. بينما يتم قياس ADIPO و ADIPOR1 و MCP-1 و PAI-1 و FSH و LH في المصل بواسطة تقنية الاليزا(ELISA).

تم تحديد البروتين احادي الخلية الكيميائي 1 (MCP-1) للعلامة المؤيدة للالتهابات في مجموعة مرضى السكري الذين يعانون من السمنة المفرطة ، ومجموعة مرضى السكري غير المصابين

بالسكري ، والمجموعات الاصحاء. أظهرت النتائج زيادة معنوية (P <0.05) في تركيز مرضى السكري الذين يعانون من السمنة المفرطة بالمقارنة مع مجموعة البدينين الأصحاء ومجموعة الأصحاء غير البدينين.

العوامل المضادة للالتهابات الاديبونكتين ومستقبله انخفضت بشكل غير ملحوظ في المرضى الذين يعانون من السمنة المفرطة مقارنة بغير البدينين ، (p <0.05). المرضى غير المصابين (P <0.05) بشكل فردي.

تتم مقارنة مستويات Malondialdehyde (MDA) و مضادات الأكسدة الكلية (TAC) ومستويات حالة الأكسدة الكلية (TOS) بين مجموعات مختلفة للمرضى والاصحاء. المرضى الذين يعانون من السمنة لديهم نسبة منخفضة من TAC مع ارتفاع MDA و TOS عالية مقارنة بالمرضى غير المصابين بالسمنة ، والذين يعانون من السمنة.

النتيجة: مرضى السمنة لديهم انخفاض FBG (172.71 ± 63.15) ، ارتفاع HbA1C (9.44 ± 1.38) ، مع مؤشر كتلة الجسم (± 33.543.31) مقارنة بالمرضى غير البدينين FBG (201.59 ± 69.66)، HbA1C (9.23 ± 1.16) ، مؤشر كتلة الجسم (25.37 ± 2.53) ، وفقًا للمعايير مقارنةً بالتحكم في السمنة (81.22 ± 15.52) FBS، HbA1C (4.93 ± 0.75) ، مع مؤشر كتلة الجسم (32.97 ± 2.99) مقارنةً بغير البدينين (81.10 ± 10.14) FBS، (5.71) HbA1C ± 0.78) ، مع مؤشر كتلة الجسم (22.42 ± 2.82). المرضى الذين يعانون من السمنة لديهم نسبة منخفضة من (0.56 ± 0.21) TAC مع MDA عالي (2.95 ± 1.52) و TOS مرتفع (1.23 ± 0.52) مقارنة بالمرضى غير البدينين (0.82 ± 0.22) TAC مع (1.33 ± 0.55) MDA) و TOS (0.81 ± 0.34)) ، على التوالي مقارنة بالتحكم في السمنة (0.64 ± 0.14) TAC مع (1.22 MDA ± 0.48) و (1.11 ± 0.45) TOS) مقارنةً الاصحاء غير البدينين (1.08 ± 0.50) TAC مع MDA (1.22 ± 0.48)) و (0.83 ± 0.25) TOS)). مرضى ADIPO الذين يعانون من السمنة المفرطة (13.37 ± 3.91) مقارنة بالمرضى غير البدينين (16.55 ± 3.21) ، الاصحاء البدينين (17.00 ± 3.87) ، غير البدينين (23.20 ± 5.10). مرضى ADIPO / R1 البدينين (14.01 ± 5.32) مقارنة بالمرضى غير البدينين (18.58 ± 1.40) ،الاصحاء البدينين (20.16 ± 2.44) ، غير البدينين (24.59 ± 4.04). MCP-1 مرضى السمنة (329.01 ± 117.52) مقارنة بالمرضى غير البدينين (100.19 ± 8.97) ، الاصحاء غير البدينين (75.20 ± 9.12) ، البدينين (95.97 ± 12.57). مثبط

تنشيط البلازمينوجين -1 (PAI) مرضى السمنة (6.25 ± 2.34) مقارنة بالمرضى غير البدينين (4.03 ± 2.23) ، الاصحاء البدينين (3.49 ± 0.94) ، غير البدينين (0.72 ± 0.16).

الخلاصة أكدت النتائج الحالية أن مستويات مصل الاديبونكتين ومستقبلة وبروتين احادي الخليه ومثبط البلازمنوجين امكن تقديمها كعوامل مبكره للسمنة السكرية وعامل خطر لتصلب الشرايين بروتين احادي الخليه يتم تحديده في مجموعة مرضى السكري الذين يعانون من السمنة المفرطة ، مجموعة غير مصابين بمرض السكري ، ومجموعات الاصحاء. أظهرت النتائج زيادة معنوية (P 0.05>) في تركيز مرضى السكري الذين يعانون من السمنة المفرطة بالمقارنة مع مجموعة البدينين الأصحاء ومجموعة الأصحاء غير البدينين.

تم الحصول على ارتباطات سلبية كبيرة بين مرضى السكري الذين يعانون من السمنة المفرطة بين الاديبونكتين ومستقبله مع تقدم العمر ، مستوى السكر الصائم ، مؤشر كتله الجسم، T.Gوقياس الدهون ، ، LDL-C البروتين الدهني منخفض الكثافة وvLDL-C ، PAI-1، MDA TOS و بينما ، الارتباطات الإيجابية التي تم الحصول عليها من هرمونات LH ، FSH و TAC و HDL-C.

شملت الدراسة الحالية 30 مريضًا مصابًا بالسمنة السكري و 30 مريضًا مصابًا بالسكري غير مصابين بالسمنة (تم اختيارهم من مركز السكري والغدد الصماء في منطقة الحلة ، بابل ، العراق ، مستشفى المرجان التعليمي) 15 من الاصحاء ذات السمنة المفرطة و 15 اصحاء غير بدناء . المجموعات الأربع غير متطابقة مع العمر.

لوحظ زياده معنويه في مستويات الكولسترول و LDL-C و VLDL-C و الدهون الثلاثية في مجموعة مرضى السكري الذين يعانون من السمنة المفرطة بالمقارنة مع مجموعة البدينين الأصحاء ومجموعة الاصحاء غير البدينين . ووجد زياده معنوية في مستويات الكولسترول و LDL-C و VLDL-C و الدهون الثلاثية لوحظ في مجموعة مرضى البدينين عند مقارنتهم مع مجموعة البدينين الأصحاء ومجموعة الاصحاء غير البدينين بينما لا يوجد تغير معنوي في مستويات HDL-C في هذه المجاميع الأربعة.

المعيار الالتهابي احادي الخليه (MCP-1) يزداد تركيزه في المرضى السكر البدينين عند مقارنتهم مع مرضى الغير بدينين ومجموعه السيطره كذالك النتائج في السيربين المثبط PAI-1. .

الخلاصة

تم مقارنه مضادات الاكسده الكليه TAC وحاله الاكسده الكليه TOS والمالون ثناي الدهايد بين المجاميع المختلفه للمرضى والاصحاء . المرضى الذين يعانون من السمنه لديهم TAC منخفضه مع MDA و TOS عالية مقارنة

تم الحصول على علاقه عكسيه معنوية لمرضى السمنة السكري بين ADIPO و ADIPOR1 مع Age و FBS و BMI و T.G و ADIPO و MDA و LDL و PAI-1 و TOS وVLdl. بينما تم الحصول على الارتباطات ايجابيه من LH و FSH و TAC و HDL

تم الحصول على ارتباطات ايجابيه معنوية لمرضى السكري الذين يعانون من السمنة المفرطة بين MCP-1 و PAI مع Age و FBS و BMI و T.G و MDA و LDL و و TOS و Vldl. بينما تم الحصول على الارتباطات سلبيه من LH و ADIPO و FSH و TAC وADIPO و HDL.

الاستنتاجات :تشير النتائج الحالية أن مستويات مصل MCP-1 و PAI-1 و ADIPO و ADIPOR1 قد تعطي علاقه جيده لتشخيص للإصابة بمرض السكر نتيجة السمنة.

Summary

Background: Type 2 diabetes mellitus (T2DM) accounts for around 90% of all cases of diabetes. In T2DM, the response to insulin is diminished, and this is defined as insulin resistance. During this state, insulin is ineffective and is initially countered by an increase in insulin production to maintain glucose homeostasis, but over time, insulin production decreases, resulting in T2DM.

Obesity is now so common within the world's population that it is beginning to replace undernutrition and infectious diseases as the most significant contributor to ill health it is caused by a mixture of excessive nutrition intake, lack of bodily activity and genetic defenselessness. An insufficient case are caused principally by genetic factor, endocrine complaints, medicines or psychological disorders. In Iraq, the occurrence of T2DM in obese persons is increasing and shows a great load on the public health and socioeconomic growth.

Aims: The current study aims to measure some cytokines related to obesity including MCP-1, ADIPOR1 and ADIPO in control individuals, diabetic obese individuals and diabetic non obese patients. Further; the study involved estimated serum levels of malondialdehyde(MDA), total antioxidants capacity (TAC) and total oxidant Status (TOS) and to find out a possible relationship between these markers and other parameters also estimated such as;body mass index BMI, fast blood glucose FBS, and lipid profiles.

Methods: The case control study design consists of 30 diabetic obese patients and 30 diabetic nonobese patients, 15 obese control and 15 nonobese control. The four groups are not matched for age. Fast blood glucose FSG, malondialdehyde (MDA), lipid profile, TAC and TOS are determined by colorimetric method. While ADIPO,ADIPOR1,MCP-1,PAI-1,FSH and LH are measured in sera by (ELISA) technique.

Pro-inflammatory marker Monocyte chemoattractant protein 1 (MCP-1) is determined in diabetic obese patients group , diabetic nonobese group , and healthy groups. The results show a significant ($P<0.05$) increase in the concentration of diabetic obese patients when compared with the healthy obese group and healthy non obese group.

Anti-inflammatory markers Adiponectin, Adiponectin Receptor 1 (ADIPO, ADIPOR1) is nonsignificantly decreased in patients obese compared to obese controls, ($p< 0.05$). nonobese patients ($p<0.05$) individually .

Result: Obese patients have low FBG (172.71±63.15), high HbA_{1C} (9.44±1.38), with BMI(33.543.31±) compared to non obese patients FBG (201.59±69.66), HbA_{1C}(9.23 ± 1.16), with BMI(25.37±2.53), according to criteria compared to obese control FBS (81.22±15.52), HbA1C(4.93± 0.75), with BMI (32.97±2.99) compared another non obese control FBS(81.10±10.14), HbA1C(5.71 ± 0.78), with BMI (22.42±2.82). Obese patients have low TAC (0.56±0.21) with high MDA (2.95±1.52) and high TOS (1.23 ±0.52) compared to nonobese patients TAC (0.82±0.22) with MDA (1.33±0.55) and TOS (0.81±0.34), respectively compared to obese control TAC (0.64±0.14) with MDA (1.22±0.48) and TOS (1.11±0.45) compared another nonobese control TAC (1.08±0.50) with MDA (1.22±0.48) and TOS (0.83±0.25). ADIPO Obese patients (13.37±3.91) compared to non obese patients (16.55±3.21), obese control (17.00±3.87), non obese control (23.20±5.10). ADIPO/R1 Obese patients (14.01±5.32) compared to non obese patients (18.58 ±1.40), obese control (20.16±2.44), non obese control (24.59±4.04). MCP-1 Obese patients (329.01±117.52) compared to non obese patients (100.19±8.97), obese control (75.20±9.12), non obese control (95.97±12.57). Plasminogen activation inhibitor-1 (PAI) Obese patients (6.25±2.34) compared to non obese patients (4.03±2.23), obese control (3.49±0.94), non obese control (0.72±0.16).

Conclusion The present results confirmed that serum MCP-1,PAI-1, ADIPO and ADIPOR1levels might be presented as novel markers for diabetic obese and risk factor for atherosclerosis Pro-inflammatory marker(MCP-1) is determined in diabetic obese patients group , diabetic nonobese group , and healthy groups. The results show a significant ($P<0.05$) increase in the concentration of diabetic obese patients when compared with the healthy obese group and healthy non obese group.

Significant negative correlations of diabetic obese patients are obtained between ADIPO and ADIPOR1 with age, FBS, BMI, T.G, MDA ,LDL-C low-density lipoprotein, PAI-1 , TOS and vLDL-C While, positive correlations obtained from LH, FSH, TAC, and HDL-C. high-density lipoprotein significant positive correlations of diabetic obese patients are obtained between MCP-1 and PAI with age, FBS, BMI, T.G, MDA, LDL-C, TOS and vLDL-C very low-density lipoprotein. While, negative correlations obtained from LH, ADIPOR1 , ADIPO, FSH, TAC, and HDL-C.

Anti-inflammatory markers (ADIPO,ADIPOR1) is significantly decreased in patients obese compared to obese controls, ($p< 0.05$) nonobese patients ($p<0.05$) individually .

Malondialdehyde (MDA), Total Antioxidants Capacity (TAC) and Total Oxidant Status (TOS) levels are comparison between different groups for patients and controls. Obese patients have low TAC with high MDA and high TOS compared to nonobese patients, obese & nonobese control.

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ABBREVIATIONS	
Abbreviation	Details
A A	Amino acid
AD	Adipolin
ADIPO	Adiponectin
ADIPOR1	Adiponectin Receptor 1
ATM	Adipose tissue macrophage
BAT	Brown adipose tissue
BMI	Body mass index
CNS	Central nervous system
COX	cyclooxygenase
CVD	Cardio vascular disease
DM	Diabetes mellitus
EC-SOD	Extracellular Superoxide Dismutase
ELISA	Enzyme-Linked Immunosorbent-Assay
FBS	Fasting blood Sugar
FFA	Free fatty acids
FSH	Follicle Stimulating Hormone
HDL-C	High density lipoprotein cholesterol
IR	Insulin resistance
LDL-C	Low density lipoprotein cholesterol
LH	Luteinizing Hormone
MCP-1	Monocyte chemoattractant protein 1
MDA	Malondialdehyde
nm	Nanometer
PAI-1	Plasminogen activation inhibitor-1
PCOS	polycystic ovarian syndrome

T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TAC	Total Antioxidants Capacity Assay
TBA	Thiobarbituric Acid
TC	Total cholesterol
TCA	Trichloroacetic Acid
TG	Triglyceride
TOS	Total Oxidant Status
UV.	Ultra violet-Visible
VLDL-C	Very low density lipoprotein cholesterol
WAT	White adipose tissue
WHO	World Health Organization

1.Introduction

1.1. Diabetes Mellitus

1.1.1. Definition

Diabetes mellitus DM is a group of metabolic disorders described with chronic hyperglycemia arising from disorders in insulin secretion, insulin action, or both. The presence of these consequences in chronic hyperglycemia led to damage, dysfunction, and failure of some organs, principally eyes, kidneys, heart, nerves, and blood vessels (Bhatti, *et al.* 2022).

Type two Diabetes mellitus T2DM is distinguished by insulin insensitivity because of insulin resistance (Henquin, 2004; Choi, *et al.* 2021)

At this point, glucose production in the liver pancreatic insulin synthesis falls below normal levels throughout time (Crewe, *et al.* 2022). T2DM patients' bodies have such little insulin, which prevents ketone generation. Hyperosmolar can develop after long periods of poorly controlled blood glucose levels (Delaney, *et al.* 2000). High blood glucose levels cause increased glucose in the urine, which is accompanied by a significant volume of water, resulting in electrolyte imbalance and acidosis Diabetes is also accompanied by microvascular and macrovascular problems (Oku, *et al.* 1999; Kazemi-Bonchenari, *et al.* 2022).

Metabolic syndrome is thought to be caused by obesity. Where obesity in adulthood is characterized by the occurrence of hypertrophy of adipocytes. In the regulation of energy homeostasis, adipose tissue is involved as an important endocrine organ and secretes several “bioactive lipoproteins (Sakers, *et al.* 2022)

Symptoms of noticeable hyperglycemia consist of polyuria, polydipsia, weight loss, sometimes with polyphagia, and distorted vision. Deficiency of

growth and susceptibility to certain infections may also be associated with chronic hyperglycemia. (Bhatti, *et al.* 2022).

The human body fails to produce insulin through the pancreas or the body is unable to move blood glucose efficiently across cell membranes to be used (Alipio, *et a*, 2010; Ali, 2011).

The food we eat is broken into smaller molecules such as oligo or monosaccharides especially glucose which is the main source of energy for the human body the glucose enters the bloodstream and is the main source of energy, But this glucose cannot enter cells without sufficient insulin being present in the body (Penney, and Kotchoni, 2022; Gheitasi, *et al.* 2022).

1.1.2. Epidemiology

The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. (Boyle, *et al.* 2010; Ozougwu, et al. 2013; Reed, J.,*et al.* 2021). Although the prevalence and incidence of T2DM vary between countries, T2DM is still considered to be a global disease. T2DM used to be considered as a disease induced by 'western lifestyles' (highcalorie diets and sedentary lifestyles) (Thompson, and Kanamarlapudi, 2013). Interestingly, the rise in prevalence of T2DM is high in developed countries (Weng, *et al.* 2016).This is thought to be due to developing countries adopting 'western lifestyles' and the increase in obesity and the number of people being overweight in their populations(Wild, *et al.* 2011; Misra, *et al.* 2022).

The long–term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, and charcot joints, people with diabetes are at increased risk

of cardiovascular, peripheral vascular and cerebro vascular disease (WHO 1999) (Bagdade, *et al*. 1967). Furthermore, due to changes in routines that induce a decrease in regular exercise and advanced obesity, the incidence of DM is increasing in the European population (Hoogeveen, 2022).

1.1.3. Classification:

Classification of Diabetes Mellitus Diabetes can be classified according to the general categories (ADA, 2017)

1.1.3.1. Type I Diabetes Mellitus:

Also known as insulin dependent diabetes (IDDM), is consequent to an unfit insulin secretion resulting from a acute decrease in the number of beta-cells in the islets of Langerhans (Mahesh, *et al.* 2022).

This type results from the body's inability to produce insulin, and continuously requires the person to inject insulin, (Donnell, E., and O'Donnell, 2019).

There is unknown protective measure against IDDM, which causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when starting occurs. Vulnerability and responsiveness to insulin are usually normal, especially in the early stages. IDDM can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of the diabetes cases in children (Meneghini, 2020).

This type is due to β-cell destruction, always leads to absolute insulin deficiency (ADA, 2017 ; suman., 2014).

A- Immune-Mediated Diabetes

This type of diabetes accounts for only 5-10% of people with diabetes, which has already been included in the term insulin-dependent diabetes, juvenile-onset diabetes or Type I diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. In this form of diabetes, the rate of *β*-cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Type I diabetes is predictable to be an autoimmune disease designated by metabolic features, genetic, and immunological. The incidence of diabetes-associated auto antibodies (DAA) and acute loss of insulin secretion can cause a severe hyperglycemia and ketoacidosis (Qadir. 2016)

B- Idiopathic Diabetes

Some characteristics of the first type of diabetes have no known causes. Some of these patients have a persistent insulin deficiency and are exposed to ketone acid, but have no evidence of autoimmunity. Individuals with this form of diabetes suffer from episodic ketoacidosis and exhibit varying degrees of insulin deficiency between episodes. The fluctuating autoantibody status remains partly understood, but possibly time-varying anti-idiotypic antibodies might affect DAA assays. Both types of DMT1 arise from the damage of *β*-cells (Morales, *et al.* 2022).

1.1.3.2.Type 2 diabetes Mellitus:

Type II diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. This form of diabetes comprises 90–95% of diabetes cases, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency (AD, 2018) Type II DM compares with type I DM diabetes, there is no autoimmune destruction of *β*-cells and subjects do not need insulin usage to survive, which comprises

individuals who have insulin resistance and typically have been relative instead of absolute insulin absence *(*Tripathi, B., and Srivastava. A., 2006).

The combination of some environmental factors such as excessive dietary intake, genetic predisposition and physical inactivity results with the occurrence of a dipocytogenesis, lipodystrophy and obesity which increase the development risk of insulin resistance. Insulin resistance predates pancreatic beta cell dysfunction and plays a crucial role in causing type II diabetes (Aleem,et al. 2018). The combination of genetic predisposition and some environmental factors demonstrated in this Figure (1-1)

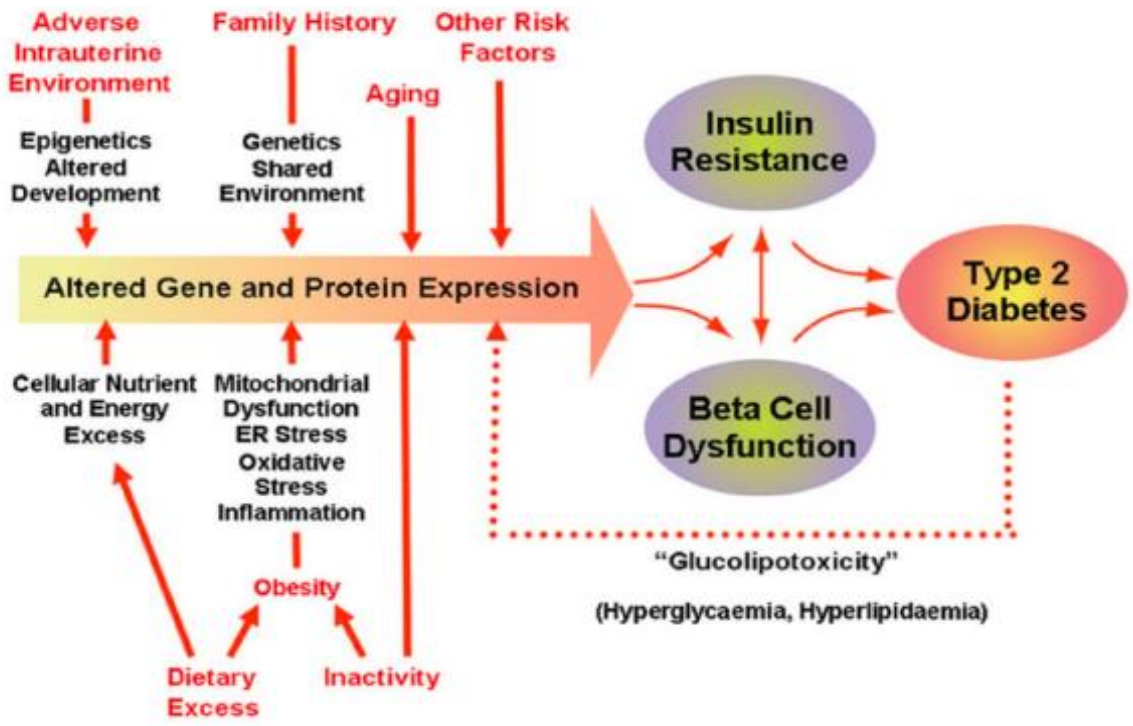


Figure 1-1: General overview of genetic and environmental factors contributing to the development of insulin resistance and type II diabetes (Jin, 2009).

1.1.3.3. Gestational Diabetes Mellitus (GDM)

"Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes" (Guillausseau, *et al*., 2008).

1.1.3.4 Specific Types of Diabetes

Pathophysiological classification of Diabetic mellitus (American Diabetes Association, 2014)

1-Genetic defects of β-cell function:

a. MODY1(mutation of hepatocyte nuclear transcription factor- 4α).

b. MODY2(mutation of glucokinase).

c. MODY3(mutation of hepatocyte nuclear transcription factor- 1α).

2-Pancreatic diseases: pancreatic neoplasm, pancreatitis, pancreatectomy and others (Fowler, 2008).

3-Endocrine causes like Cushing syndrome, acromegaly and others

4-Drug that induce DM for example glucocorticids, β-Adrenergic agonists and others

5-Infections: cytomegalovirus, rubella and others

1.1.4. Diagnosis of Type 2 Diabetes

American Diabetes Association was proposed the essential criteria for analysis of the infection with type 2 the clarification of the criteria include (AAD, 2014): An obese person (>120% desirable body weight or body mass index >25

kg/m2) who has a first-degree relative with DM and have other risk factor such as:(AAD2018)

1. History of cardiovascular disease.
2. First degree relative with diabetes.
3. Hypertensive (blood pressure >140/90).
4. High risk ethnic population (Asian American, Native American, Latino, African American). HDL ≤ 35mg/dl or triglyceride ≥ 250 mg/dl
5.

1.1.5. Genetics of Type 2 Diabetes

About 90% of all diabetes patients result from complex interplay between genetic, epigenetic and environmental factors. Identification of the genetic factors has been a challenge because the interaction between environmental factors, diet and activity level (Rhea, et al. 2022).

In recent years, there has been an expansion of genetic variants in danger and defense of T2D due to the technical evolution that allowed genome-wide association studies and next-generation sequencing. Today, more than 120 variants have been convincingly replicated for their relationship with T2D and many more with diabetes-related characters (Andreadi, et al. 2022).

1.1.6. Causes of Type 2 Diabetes Mellitus

It is believed that genetics plays a much larger role in type 2 diabetes than in type 1 diabetes. Thus, the environment plays a smaller role (Guariguata, *et al.* 2014; Shahwan, *et al.* 2022). T2DM is principally attributable to lifestyle factors. The associated of lifestyle with hereditary factors lead to the progress of T2DM (Thompson. and Kanamarlapudi, 2013).

A number of these factors are under individual control such as diet and obesity, physical inactivity and smoking, while other reasons are not such as increasing age, female gender. It is worth mentioning that the relationship between low birth weight and insulin resistance has attracted attention. These reasons are reflected the major risk factors for T2DM (Kahn, *et al.* 2014; Nibali, *et al.* 2022;).

1.1.7.Complications of Diabetes Mellitus

The risk of developing the complications of diabetes reduced when early identify and treatment of diabetes. The results of uncontrolled diabetes such as impairment to the kidneys, eyes, nervous system, heart, gums ,teeth , skin ,feet and blood vessels. Complications of diabetes are due to pathologic changes that involve peripheral nerves, large blood vessels, peripheral nerves cranial, the lens of the eye and the skin.

Microvascular complications of diabetes include nephropathy, neuropathy and retinopathy. Macrovascular complications involve damage to the heart, extremities, and large blood vessels of the brain (Riddell, and Peters, 2022) The complication of DM are represented in the following Figure (1-2)

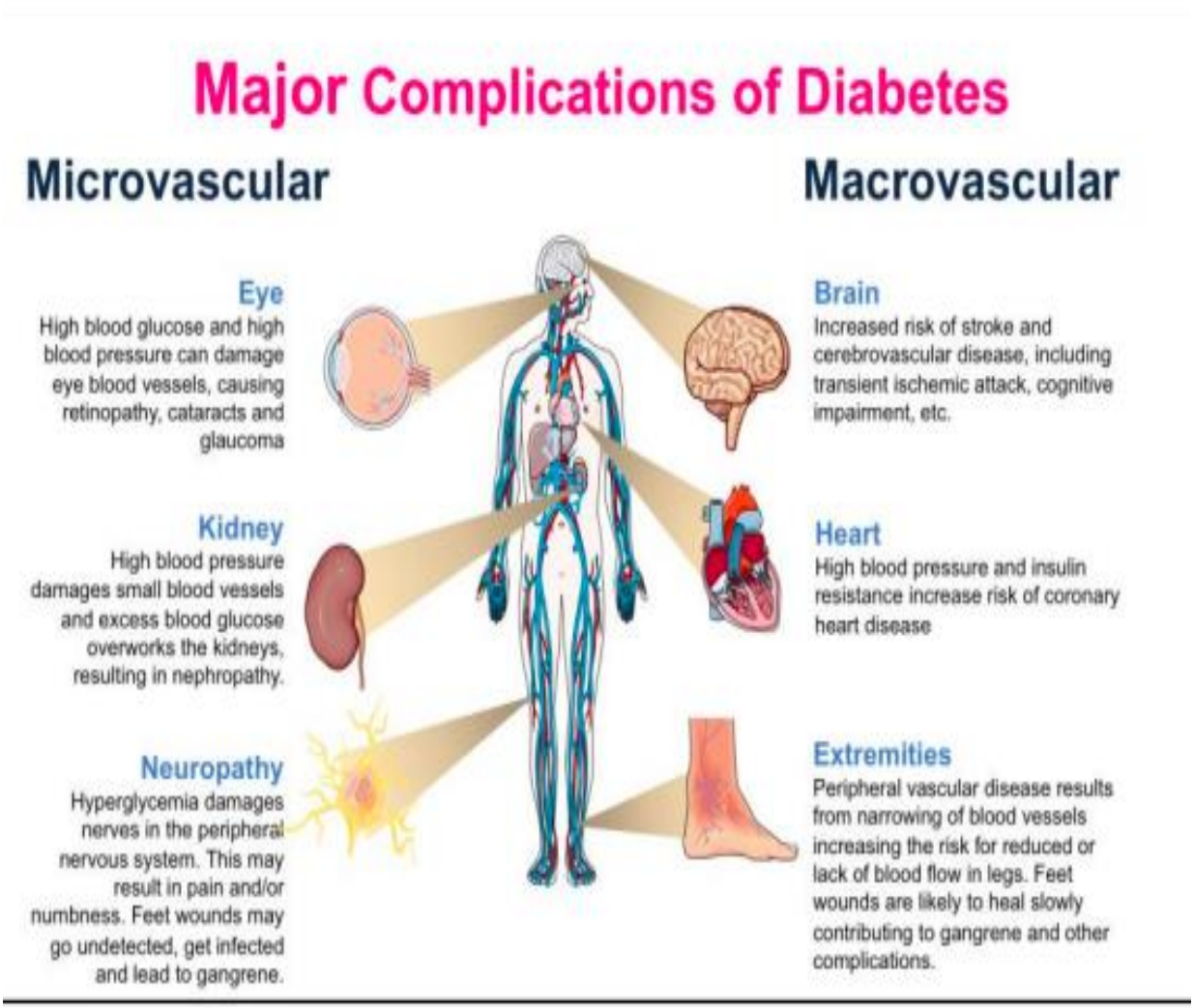


Figure 1-2: Diabetic Complication. (https://pdb101.rcsb.org/global-health/diabetes/mellitus/monitoring/complication).

1.1.8.Type 2 Diabetes Mellitus and obesity

Given that ~90% of patients are obese or overweight at T2DM diagnosis, the aetiology of T2DM is largely thought to be linked to diets involving excessive nutrient consumption combined with insufficient energy expenditure (Chen, *et al*. 2012; Reed, *et al.* 2021 ; DeFronzo, `*et al.* 2013; Prasad, *et al*. 2022). Despite this, post-diagnosis complications, especially long-term complications, are prevalent globally. As a result, diabetes remains a leading cause of blindness,

end-stage renal disease, lower limb amputation and cardiovascular disease (Thompson. and Kanamarlapudi, V., 2013; Pozo Garcia, *et al.* 2022).

T2DM and obesity have such an interdependent relationship that the term "diabesity" has been coined (Golay, and Ybarra, 2005; Shah, *et al.* 2022). In recent decades, the number of people with T2DM has more than doubled. T2DM is thought to be largely due to an increase in obesity (Haslam, D., 2010; Saad, *et al.* 2022). Obesity has become a global pandemic over recent decades. Weight loss is associated with an improved prognosis for overweight T2DM patients and obese individuals. Better glycaemic control has been reported in T2DM patients who have lost weight, and excess body weight is associated with the risk of cardiometabolic complications, which are major causes of morbidity and mortality in T2DM and obese individuals (Horton, *et al.* 2014; Wilding, 2014; Berman, *et al.* 2022).

Bariatric surgery has proven to be an effective treatment for diabesity, but it is expensive and there are numerous post-surgery complications: for example, vomiting and dumping syndrome, iron and B12 deficiency, and secondary hyperparathyroidism (Fujioka, 2005; Reed, *et al.* 2021). GLP-1 analogues (e.g. liraglutide and exenatide) are used to treat T2D as they promote insulin secretion and induce weight loss (Nauck, 2016). Since the GLP-1 receptor (GLP-1R) agonists are effective in treating diabesity, they could be pharmacological alternatives to bariatric surgery but without the post-surgery complications (Lok, *et al.* 2022).

The consensus in the literature is that T2DM clinical manifestation is provoked by peripheral tissue insulin resistance, which is in turn, usually induced by obesity (Karamanakos, *et al.* 2022). Obesity is characterised by elevated levels of cytokines and fatty acids, and it is thought that elevated levels of both provoke insulin resistance (Pamuk, F. and Kantarci, 2022). However, insulin

resistance is not still determined how this occurs mechanistically (Muoio, and Newgard, 2008; Tricò, *et al*. 2022). Following the induction of insulin resistance, islet *β*-cells can maintain normoglycaemia and metabolic homeostasis by increasing their secretion of insulin and/or by increasing their number (Mehran, *et al*. 2012; Wang, 2022; Zhang, Shen, 2022; Fernández-Millán, E. and Guillén, 2022).

Insulin resistance is ability to secrete insulin decreases and many islet *β*-cells undergo apoptosis, which is thought to be a result of a variety of stressors, such as increased insulin demand, oxidative, endoplasmic reticulum, dyslipidemic, amyloidal, and inflammatory stress (Boland, *et al.* 2017). The characteristic consequences of *β*-cell pathology during T2DM include impaired insulin secretion, ongoing insufficient insulin secretion to promote normolipidaemia (normal triglyceride levels, normal LDL cholesterol, and normal HDL-cholesterol) and normoglycaemia, dysfunctional glucose-sensing, and an increased proportion of proinsulin secretion (Boland, *et al*., 2017; Suleiman, *et a*, 2022).

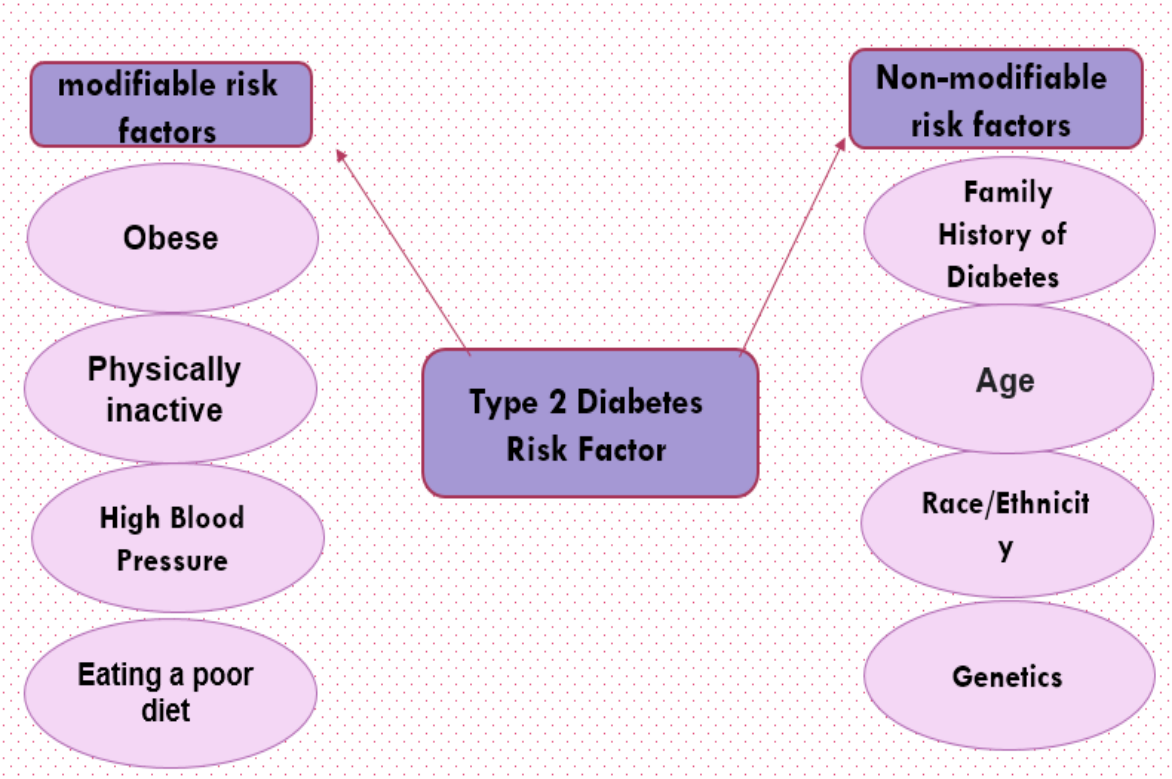


Figure 1-3 Risk Factor of T2DM

Although obesity is a major risk factor for T2DM depend on BMI, paradoxically overweight and obese patients have been reported to have had a lower mortality rate than normal-weight patients due to cardiovascular pathology associated with T2DM and this phenomenon was termed "the obesity paradox" (Levitsky, *et al.* 2022). Furthermore, weight loss has been reported to increase mortality and morbidity in T2DM and cardiovascular co-morbidity patients (Guariguata, *et al.* 2014; Bluhm, *et al.* 2022). Additionally, a study found that the risk of amputation in non-elderly diabetic men decreased with increasing body weight (Al Yafi, *et al.* 2022). Peripheral and hepatic insulin resistance is present in obese and non-obese T2D patients, but not to the same extent in non-obese subjects (Howlader, et al. 2014; Alizadeh, 2022).

Proinflammatory cytokines (Its exceptionally large and diverse group of pro- or anti-inflammatory factors that are grouped into families based upon their structural homology or that of their receptors) produced by adipose tissue as a

consequence of obesity, are known to be cytotoxic to *β*-cells, and they likely contribute to T2D pathogenesis and islet dysfunction post-diagnosis (Shahwan, *et al.* 2022). There is also evidence that these cytokines play a role in the induction of insulin resistance (Carmichael, *et al.* 2022). Thus, the adipose tissue also likely contributes to T2D aetiology/pathogenesis, but to what extent remains currently unknown. (Carmichael, *et al.* 2022). Hyperlipidaemia was increased deposition of fat into other tissues, such as skeletal muscle and liver. (Takahashi, *et al.* 2022).

The diabetic greatly increases the risk of atherosclerotic plaque formation due to dyslipidaemia in patients, which results in increased plasma levels of the small dense atherogenic form of LDL cholesterol, and these molecules can easily penetrate the arterial wall and promote atherosclerosis (Lim, and Bleich, 2022). The chronic inflammatory state associated with T2DM is also thought to encourage plaque growth and formation (Keeter, *et al.* 2022).

The impaired insulin secretion and action induce pathology in the microvasculature, as nitric oxide (NO) production is dependent upon insulin signalling (Cohen, *et al.* 2022). Chronic NO-deficiency in T2DM results in a hyper-constricted state of the microvasculature; therefore, the delivery of oxygen and nutrients to tissues is impaired, contributing to diabetic neuropathies and the poor exercise tolerance observed in patients, as well as elevated blood pressure (Zhu, *et al.* 2019 ;Reed, *et al.* 2021).

1.1.9. Etiology of Diabetes Mellitus

1.1.9.1. Environmental Factors

Several environmental factors play a role in increasing the risk of T2DM, including nutrition, lack of physical activity, obesity, stress, exposure to

pollutants, and changing lifestyle(Ardisson Korat, *et al.* 2014; Kyrou, *et al.* 2018; Barbagallo , *et al* ,2022)

1.1.9.2. Genetic Factors

The increased risk of developing T2DM for relatives of type 2 diabetic patients may be due to them sharing similar diets and lifestyles as well as genetics (Lembo, *et al.* 2022, Saad, B., *et al.* 2022). T2DM susceptibility independently of the diet as there was a higher prevalence of the disease in the twin population compared to the singleton population (Periñán, M., *et al.* 2022; Zhang, *et al.* 2022; Broni, E., *et al.* 2022).

1.1.10.Type 2 Diabetes Treatment

Managing T2DM includes a mix of lifestyle changes and medication.

1.1.10.1. Lifestyle changes

People with DM are obliged to take important daily decisions concerning their treatment but are often also required to make lifestyle changes with regard to their dietary patterns and level of physical activity in order to prevent or manage concomitant CVDs (Ye, 2013). Traditional modifiable risk factors for both DM and CVDs include obesity, smoking, physical inactivity, elevated blood pressure, and elevated HbA1c (Martín-Timón, 2014). Treatment and adaptation of self-care behavior in chronic diseases is a slow process, due to the need of the people in these conditions to develop knowledge on their health condition with the possibilities of promoting healthcare, dealing with the disease and preventing complications. (Thorne, *et al.* 2003; Alberti, *et al.* 2007).

1.1.10.2. Medication

The lifestyle changes don't get you to your target blood sugar levels, you may need medication (Asif, 2014).

Metformin is a biguanide that has been used worldwide for the treatment of type 2 diabetes for the past 4 decades. It improves glycemic control by enhancing insulin sensitivity in liver and muscle. Metformin does not stimulate insulin secretion and therefore is not associated with hypoglycemia (Cusi, and DeFronzo, 1998). Improved metabolic control with metformin does not induce weight gain and may cause weight loss. Metformin also has a beneficial effect on several cardiovascular risk factors including dyslipidemia, elevated plasminogen activator inhibitor 1 levels, other fibrinolytic abnormalities, hyperinsulinemia, and insulin resistance. metformin has been reported to decrease lipid oxidation and plasma free fatty acid levels. Metformin monotherapy decreases the fasting plasma glucose concentration by ~ 60-70 mg/dl and HbA1c by 1.5-2.0% in patients with T2DM (Bailey, C. J.2017; Chaudhury, *et al.* 2017).

1.1.11. Pathophysiology of Type2 DM

The individuals with impaired glucose tolerance have hyperglycemia in spite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion (Abdul-Ghani, *et al.* 2006; Ozougwu, *et al.* 2013).

Most patients with the common form of NIDDM have both defects. Recent evidence has demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of T2DM (Kadowaki, T., 2000 ; Zhou, and Xu, 2022).

1.1.12. Pathogenesis

The main focus here is the current and future therapeutic potential of modulation of GLP-1R activity in T2DM, but the altered activity of hormones involved in metabolic homeostasis observed in T2DM such as the nervous system and uncoupling protein 2 (UCP2), to highlight the complexity of its pathogenesis (Reed, *et al.* 2021). Typically, T2DM does not manifest acutely in individuals but is preceded by an insidious phase of prediabetes (van Duinkerken, and Ryan, 2020). Prediabetes is characterised by raised blood glucose levels (fasting plasma glucose levels of 6.1–6.9 mmol/L and two hours post glucose ingestion levels between 7.8–11 mmol/L) due to declining islet beta-cell mass and function but not enough to warrant a diagnosis of T2DM (Reed, *et al.* 2021).

1.1.13. Glycated Hemoglobin (HbA1c) with diabetes mellitus

The WHO Consultation found that HbA_{1C} can be used as a diabetes diagnostic test if severe quality assurance tests are in place and assays are standardised to worldwide reference requirements. There are no criteria that would prevent it from being accurate measurement (weykamp,2013).

HbA1c is a measurement of mean plasma glucose over the preceding eight-week (Nathan, *et al.* 2007). It can be done at any time of day and does not necessitate any kind of specialized preparation, such as fasting. Because of these characteristics, the primary test determines glycaemic control in diabetics. Recently, there has been a lot of interest in using it as a diabetes diagnostic test and as a diabetes screening test for people who are at high risk of developing diabetes. Other biochemical tests for T2DM such as random blood sugar Test (Casual), fasting blood sugar test and glucose tolerance test (Nathan, 2014).

1.2. Obesity

Obesity is now so common within the world's population that it is beginning to replace undernutrition and infectious diseases as the most significant contributor to ill health (Kopelman, 2000). In particular, obesity is associated with diabetes mellitus, coronary heart disease, certain forms of cancer, and sleep-breathing disorders (Du, *et al.* 2022).

Obesity is defined by a body-mass index (weight divided by square of the height) of 30 kg/ m^2 or greater, but this does not take into account the morbidity and mortality associated with more modest degrees of overweight, nor the detrimental effect of intra-abdominal fat (Anzueto, *et al.* 2011). The global epidemic of obesity results from a combination of genetic susceptibility, increased availability of high-energy foods and decreased requirement for physical activity in modern society (Astrup, 2001). Obesity should no longer be regarded simply as a cosmetic problem affecting certain individuals, but as an epidemic that threatens global wellbeing (Bozkurt, *et al.* 2013).

The classification of obesity differs in terminology. The criteria for the diagnosis of underweight, overweight, and obese adult in accordance with the BMI are explained in Table 1-1 (WHO Classification. 2016).

Table 1-1: The Classification of Obesity

Classification	BMI(Kg/m^2)
	Principal Cut-off points
Sever thinness	<16.00
Moderate thinness	16.00-16.99
Mild thinness	17.00-18.49
Underweight	<18.50
Normal range	18.50-24.99
Overweight	≥25.00
Preobese	25.00-29.99
Obese	≥30.00
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	≥40.00

Based on their morphology and functions, the Adipose Tissue (AT) is divided into two depots: white (WAT) and brown (BAT). The WAT consists of cells with a single big lipid droplet, which, in reaction to the calorie, are called unilocular cells (Al-Ameri, and AM AL-Mashhedy, 2021).

Obesity, a chronic condition characterized by adipose tissue growth and inflammatory components, has been associated to the development of a number of metabolic illnesses (Jung, and Choi, 2014).) Insulin resistance and metabolic syndrome are more frequent in people who have abdominal obesity and excess visceral adipose tissue (VAT). VAT plays a critical role in obese inflammation (Van Greevenbroek, *et al.* 2013).

1.2. 1. Types of Obesity

There are three types of obesity.

1.2.1.1. Monogenic Obesity

Monogenic obesity is described as rare and severe early-onset obesity with abnormal feeding behavior and endocrine disorders, this is mainly due to autosomal recessive mutations in genes of the leptin-melanocortin pathway which plays a key role in the hypothalamic control of food intake (Farooqi, and Rahilly, 2004).

1.2.1.2. Syndromic obesity

Syndromic obesity is obesity occurring in the clinical context of a distinct set of associated clinical phenotypes (Pigeyre, and Meyre, 2018). Over 25 syndromic forms of obesity have been identified, the genetic bases for some of these syndromes have been elucidated and are beginning to provide insights into the pathogenesis of the derangements of energy homeostasis. including Prader-Willi syndrome and Bardet-Biedl syndrome (Chung, 2012).

1.2.1.3. Common Obesity

The prevalent form of obesity is polygenetic, with no discernible pattern of inheritance. Mundelein heritage as opposed to monotonous obesity. The first study shows that genetic variables could be due rather than the environment alone to non syndromic obesity (Kushner, *et al*., 2013)

1.2.2. Obesity and Type 2 Diabetes Mellitus

Obesity is characterized by elevated fasting plasma insulin ,BMI and an exaggerated insulin response to an oral glucose load (Ahuja, *et al.* 2022). Overall fatness and the distribution of body fat influence glucose metabolism through

independent but additive mechanisms. Increasing upper body obesity is accompanied by a progressive increase in the glucose and insulin response to an oral glucose challenge with a positive correlation being observed between increasing upper body obesity and measures of insulin resistance (Aguayo-Mazzucato, 2020; Tricò, *et al.*2022).

Different fat depots vary in their responsiveness to hormones that regulate lipolysis and this also varies according to fat distribution (Li. *et al.* 2022). In both men and women, the lipolytic response to noradrenaline is more marked in the abdominal than gluteal or femoral adipose tissue48. Cortisol may also contribute to this enhanced lipolysis by further inhibiting the antilipolytic effect of insulin (Gavin, and Bessesen, 2020; Lang, S., and Schnabl, 2020). FFAs have a deleterious effect on insulin uptake by the liver and contribute to the increased hepatic gluconeogenesis and hepatic glucose release observed in upper-body obesity (Klein, *et al.* 2022 ; Hallenborg, *et al.* 2021)

Plasma lipid profile associated with obesity by elevated fasting plasma triglyceride concentration, reduced high-density lipoprotein–cholesterol, marginal elevations of cholesterol and low-density lipoprotein–cholesterol concentrations (Gou, *et al.* 2021 ;Jeyabalan, *et al.* 2022 ;Kopelman, 2000). High BMI is one of the risk factors associated with T2DM and the unhealthy diet followed gives an inactive body Low socioeconomic status are factors that contribute to both obesity and T2DM where obesity was diagnosed when BMI measurements were used alone. (Almubarak, 2016; Sabanayagam, *et al.* 2021).

1.2.3. Lipids Profile in Obesity

Obesity is associated with elevated blood pressure, blood lipids and blood glucose levels, this also increases the risk of coronary heart disease in obese persons (Kannel, *et al.* 1991). Amongst the lipid components considerable stress

has been made on estimation of total cholesterol, HDL-C and triglycerides however other components like total lipids, LDL-C and VLDL-C along with chylomicrons have also been a point of interest for many workers. The results of total lipids clearly show much higher levels in obese persons as compared to controls (Bhatti, *et al.*2001; Hillock-Watling, and Gotlieb, 2022).

The obese subjects have the habit of overeating and less consumption of calories and also have sluggish pattern of life (Blüher, 2019). Higher levels of triglycerides found in obese persons increase statistically and correlate with the findings of Varley (Duncombe, *al*, 2022), The triglyceride levels are the most important factor leading to CHD as almost 50% of patients with asymptomatic atherosclerosis were hypertriglyceridemia. (Sarmadi, *et al.* 2021 ;Trujillo-Viera, *et al.* 2021), Chylomicron level in the blood is totally diet dependent as higher levels are seen within hours of dietary intake but after longer period chylomicron level become well below the normal limits. In the present study the samples were taken after (Miura, *et al.* 2022 ;Adorni *et al.* 2022)

In fact, LDL-C isolated from non-insulin-dependent diabetics contains more age products and conjugated dienes than native LDL-C and is more quickly oxidized by copper (Davì, *et al.* 2005). Additionally, plasma from patients with poorly controlled insulin-dependent diabetes shows a lower antioxidant capacity (Lodovici, *et al.* 2009; Toth, *et al.* 2013).

1.2.4. Adipose Tissue and Insulin Resistance

Adipose tissue is an endocrine organ that influences both glucose and lipid metabolism (Kershaw, and Flier, 2004; Scherer, 2006). by releasing adipocytes, pro-inflammatory factors, and free fatty acids (FFAs), which impair glucose metabolism and muscle ATP synthesis (Brehm, *et al.* 2006), promote the synthesis of toxic lipid metabolites, and alter insulin signaling (Scherer, 2016).

Insulin acts on adipose tissue 1) by stimulating glucose uptake and triglyceride synthesis and 2) by suppressing triglyceride hydrolysis and release of FFA and glycerol into the circulation (Saponaro, *et al.* 2015).

Adipose tissue insulin resistance (Adipo-IR), that is, the impaired suppression of lipolysis in the presence of high insulin levels, has been associated with glucose intolerance, and elevated plasma FFA levels have been shown to impair muscle insulin signaling, promote hepatic gluconeogenesis, and impair glucose stimulated insulin response (Gastaldelli, *et al.* 2017; Scheel, *et al.* 2022).

Although the role and natural history of *β*-cell dysfunction and muscle insulin resistance are well established in the development of T2DM, the impact of Adipo-IR in the transition from normal glucose tolerance (NGT) to T2DM has not been fully elucidated. The *in vivo* assessment of Adipo-IR is still controversial because many different approaches have been used to characterize Adipo-IR. By using tracers, it is possible to quantitate palmitate turnover (Sasaki, et al. 2022) and the rate of glycerol release to provide an index of lipolysis(Huang, *et al.* 2022).

1.3. Cytokines

Cytokines are a class of small proteins that act as signaling molecules at picomolar or nanomolar concentrations to regulate inflammation and modulate cellular activities such as growth, survival, and differentiation (Ramesh, *et al* ,2013).

Different types of cytokines had been discovered, including chemokines, interferons (IFN), interleukins (IL), lymphokines and tumor necrosis factor (TNF) (Ferreira, *et al.* 2018).Chemokines are a group of secreted proteins within the cytokine family whose generic function is to induce cell migration (Walz, *et al.* 1987; Yoshimura, *et al.* 1987). These “chemotactic cytokines” are involved

in leukocyte chemoattraction and trafficking of immune cells to locations throughout the body.

Chemokines belong to two categories based on their biological activity, namely, the maintenance of homeostasis and the induction of inflammation (Braoudaki, *et al.* 2022). Homeostatic chemokines are involved in immune surveillance and navigation of cells through hematopoiesis and are typically expressed constitutively (Devi, 2000).

1.3.1.The Cytokines Related to the Obesity

The production and release of inflammatory cytokines has been previously reported to be increased in visceral adipose tissue (VAT) (Fried, *et al.* 1998; Després, and Lemieux,). The anti-inflammatory adipokine adiponectin has been found to be lower in VAT compared with subcutaneous adipose tissue (SAT) (Lihn, A. *et al.* 2004 ; Neels, and Olefsky2006). It is well established that human adipose tissue has the ability to produce and secrete a variety of proteins including cytokines and chemokines, some of which are involved in the development of obesity related derangements (Cottam, *et al.* 2004; Frühbeck, and Salvador, 2004)

Obesity is considered an increased circulating fatty acid that is causing low-grade chronic inflammation due to macrophages' chemoattraction and its expansion in the adipose tissue; (Weisberg, *et al.* 2003; Ervin, 2009).

Obesity has been shown to be associated with the production of dysregulated cytokines and augment the synthesis of acute-phase reactants, such as IL-6, IL-8, TNF-α and monocyte chemotactic protein-1 (MCP-1) in patients with obesity and various animal models of obesity (Greenberg, and Obin, 2006; Schaible, and Kaufmann, 2007; Ellulu, *et al.* 2017).

1.4. Monocyte Chemoattractant Protein-1 (MCP-1/CCL2)

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages. Both CCL2 and its receptor CCR2 have been demonstrated to be induced and involved in various diseases. Migration of monocytes from the blood stream across the vascular endothelium is required for routine immunological surveillance of tissues, as well as in response to inflammation (Leonard, E., and Yoshimura, 1990; Singh, *et al.* 2021). The involvement of MCP-1 in the development of obesity, diabetes, cardiovascular disease, insulitis, diabetic nephropathy, and diabetic retinopathy is highlighted in this study (Panee, 2012).

The role of MCP-1 has been implicated in pathogenesis of various diseases where it contributes by numerous mechanisms figure: 1-4. Here we have selected some pathological conditions where MCP-1 expression has been found more predominant and enumerate their involvement based on available literature (Cushing, *et al.*1990; Singh, *et al.* 2021).

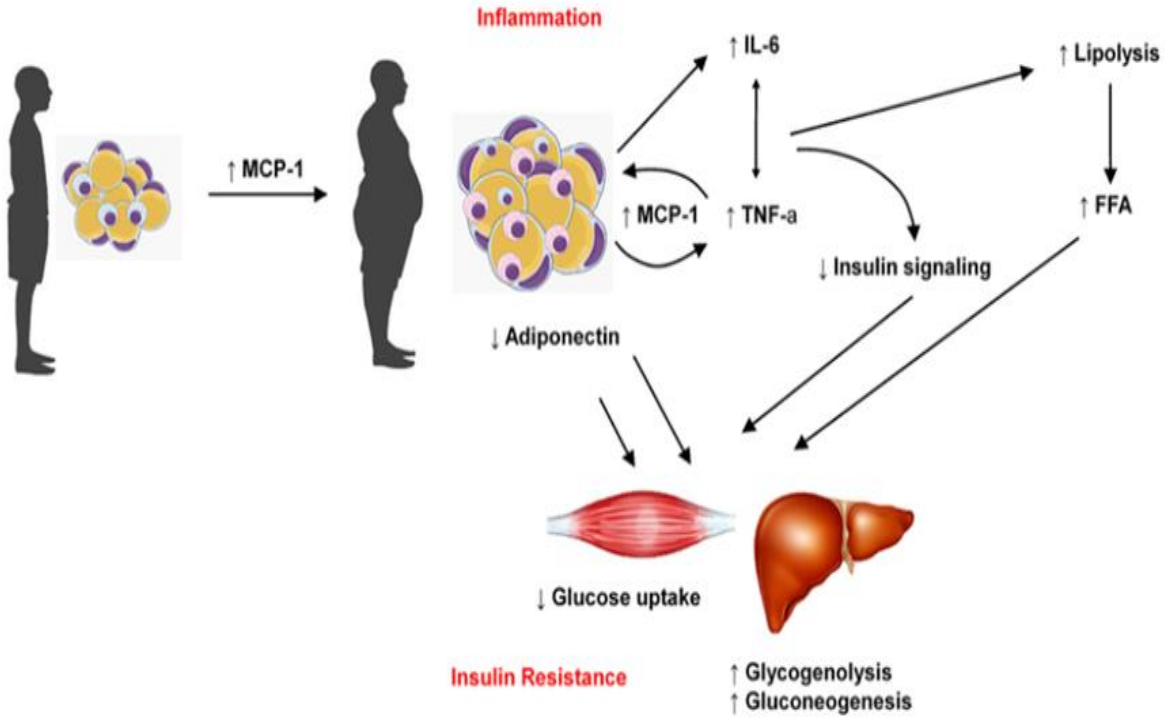


Figure 1-4 The Relationship between MCP-1 and Adipose Tissue (Freitas Lima, *et al.* 2015) Increase in adipose tissue mass is related to increase in MCP-1, which favors macrophages migration to adipose tissue and the production of other adipokines. On the other hand, obese adipose tissue produces less adiponectin. Taken together, these features reduce glucose uptake in muscle cells and favors glycogenolisis and gluconeogenesis in liver, which contribute to insulin resistance and diabetes

In white adipose tissue, simultaneous ablation of AdipoR1 and R2 resulted in elevated MCP-1 expression and the macrophage marker Mac-1 (WAT). Reduced adiponectin signaling could be an upstream mechanism for increased MCP-1 production and inflammation in WAT (Yamauchi *et al.* 2007)**.**

1.6. Plasminogen Activator Inhibitor-1 (PAI-1)

A member of the serine protease inhibitor family, has dual activity in cardiovascular and renal systems to promote both thrombosis and fibrosis, In plasma, PAI-1 promotes clot formation, which plays a key role in the

pathogenesis of myocardial infarction, stroke, and other cardiovascular events (Schäfer, *et al.* 2001; Ma, *et al.* 2004; Basak, *et al.* 2022).

1.7. Hormone Related with Diabetes and Obesity

1.7.1. Adiponectin and Adiponectin Receptor 1

Adiponectin and adiponectin receptors (AdipoRs) have been found to have important roles in chronic diseases associated with obesity (Zhang, *et al.* 2022). The functional and genetic studies confirming that adiponectin is a therapeutic target adipokine. Several interactions and roles with some other biomolecules Monocyte Chemoattractant Protein -1 (MCP-1) has been clearly identified to form a sinister adipokine network causes of obesity-related insulin resistance and metabolic syndrome; PPARγ(Peroxisome proliferator-activated receptor γ) regulates adiponectin and PPARα (Peroxisome proliferator-activated receptor α) regulates AdipoRs; dietary osmotin may act as a natural adiponectin receptor agonist.(Lu, *et al.* 2008; Natalucci, *et al.* 2021).

Adiponectin is a collagen plasma protein that is secreted by adipocytes that are responsible for the development of insulin resistance and hematological diseases. Studies have found that low protein leads to insulinomas (Gonzalez, *et al.* 2018), diabetes, atherosclerosis, and coronary artery disease. Up-regulation of adiponectin and its receptors, partly related to insulin sensitivity to antidiabetic drugs (Yamauchi, and Kadowaki, 2008). Discuss the anti-hormone antagonism of adiponectin, its association with insulin resistance and obesity, and the use of adiponectin and its receptors as a therapeutic measure (Kawano, and Arora, 2009; Abou-Samra, *et al.* 2020; Al-Ameri, and AM AL-Mashhedy, 2021).

1.7.2. Follicle-Stimulating Hormone FSH

A hormone released by the pituitary gland, FSH plays an important role in female development and reproduction by stimulating growth of the ovarian follicle before ovulation (Bhardwaj, *et al.* 2019). From menopausal transition to menopause, diminished ovarian function leads to hormonal changes characterized by decreases in reproductive hormones including estrogen, progesterone, testosterone, and inhibin B, these endocrinologic changes may result in metabolic dysfunctions such as weight gain, hyperlipidemia, hypertension, insulin resistance, and abdominal fat deposition; such changes not only serve as risk factors for MetS, but also increase the morbidity and mortality of cardiovascular disease (CVD), which is the leading cause of mortality in postmenopausal women(Lee, *et al.* 2022; Strack, *et al.* 2022).

Follicle-stimulating hormone (FSH), a glycoprotein polypeptide hormone, is one of the main gonadotropins in the human body, and is synthesized and secreted by the gonadotrophic cells in the anterior pituitary gland (Wang, *et al.* 2021). The reproductive actions of FSH in women include maturation of ovarian follicles, proliferation, and differentiation of granulosa cells, and secretion of estrogen during the menstrual cycle (Recchia, *et al*., 2021; Santoro, *et al.* 2021). The increased metabolic dysfunctions that occur during menopause coincide with changes in the levels of reproductive hormones, it is hypothesized that FSH may also be involved in these metabolic dysfunctions in postmenopausal women (Martins, *et al.* 2019; Lee, *et al.* 2022).

1.7.3. Luteinizing Hormone LH

Luteinizing hormone (LH, also known as luteinising hormone, lutropin and sometimes lutrophin) is a hormone produced by gonadotropic cells in the anterior pituitary gland (AL-azzawi, *et al.* 2022).

Optimal fat mass is necessary for normal gonadotropin levels in adults, and both undernutrition and overnutrition suppress gonadotropins thus, the gonadotropin response to relative adipose mass is biphasic , adult obesity is associated with blunted luteinizing hormone (LH) pulse amplitude that is partially attributable to increased LH clearance rate (Rosenfield, R., *et al.* 2010). LH and FSH decrease in diabetes mellitus type2 in both sexes (Hussein, and Al-Qaisi, 2012).

1.8. Cardiovascular and Atherosclerotic Complications with Diabetes and Obese

Information on overt cardiovascular complications in young people with T2DM is scarce (Choi, *et al.* 2013). Early signs of cardiovascular involvement were investigated by electrocardiography, ambulatory blood pressure measurements, and echocardiography (Cioana, et al. 2021). Hungarian children and adolescents with type 2 disease who were followed up for 1–12 years (Dart, 2010). Mean nighttime systolic and diastolic blood pressure levels were substantially higher in the group with diabetes compared with age-specifi c reference values. As many as 71% had diminished nocturnal decline in blood pressure (non-dippers), which is a known predictor of cardiovascular risk. Ultrasonographic variables indicating posterior and septal wall thickness were above the reference range in 47% of children. Ettinger and colleagues (Carchman, et al. 2005 ;Cioana, et al. 2022).

Cardiovascular disease (CVDs) was effect with obesity in different ways (Gungor, et al. 2005; Zhang, *et al.* 2022). Many adipokines mediate the cross-link between vasculature, heart and adipose tissues in the “adipo-cardiovascular axis”; the altered release of adipokines promotes a prothrombotic state contributing to atherosclerosis disease (Rega-Kaun, *et al.* 2013).

1.9. Antioxidants:

Antioxidants are substances that may keep cells from the injury caused by unstable molecules known as free radicals. Antioxidants react with stabilize free radicals and may inhibit the injury of free radicals might otherwise cause (Engwa, 2018; Gulcin, 2020).

Antioxidants have the ability to donate hydrogen atoms to free radicals that have been produced by cellular metabolism or by external sources, therefore preventing the chain reaction and causing damage to lipids, amino acids, and DNA, which ends in cell death (Lü, *et al.* 2010; Engwa, *et al.* 2022). These enzymes are often used in clinical studies to measure the antioxidant defence system. Samples are commonly collected and stored in different ways, which influences the enzyme activity and protein content or gene expression results (da Silva, *et al.* 2022).

Antioxidants (enzymatic or non-enzymatic) are classified depending on their mode of action as primary antioxidants (hydrogen or electrons donors) or secondary antioxidants (oxygen scavengers or chelating agents) (Misra, *et al.* 2014) antioxidants can also be grouped according to size, solubility, or structure show in Figure 1-5.

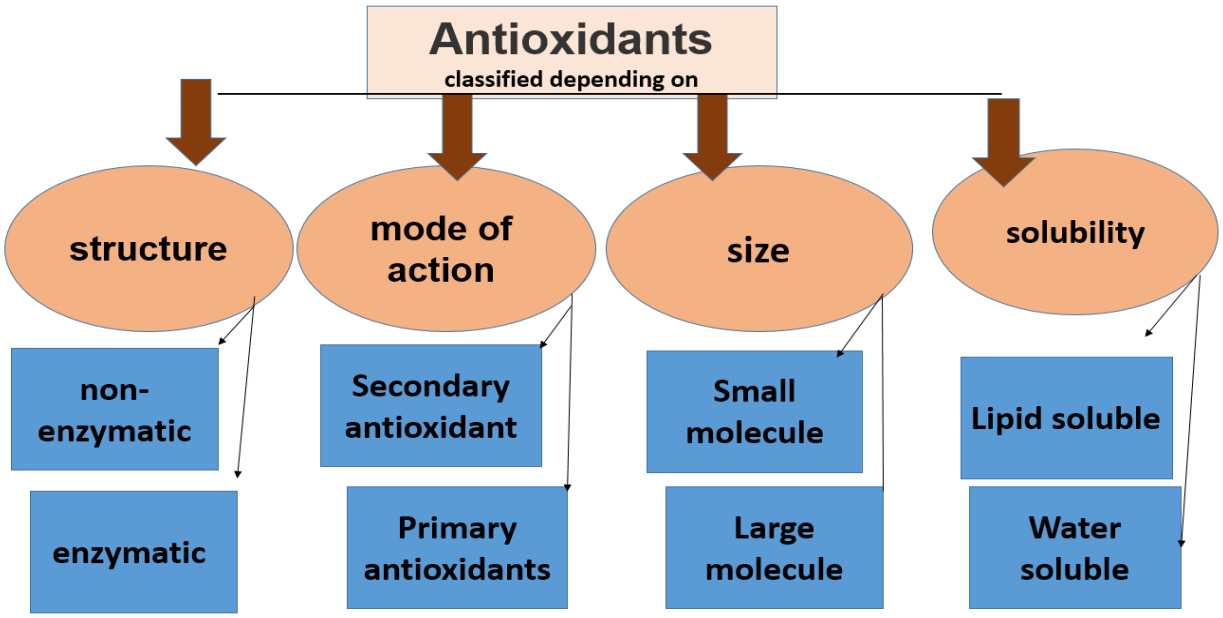


Figure 1-5 Classification of antioxidants

1.9.1. Enzymatic Antioxidants:

Enzyme processes can produce free radicals, including enzyme antioxidants:

1. peroxide dismutase (SOD)

SOD family members serve as the first line of defence against reactive oxygen species (ROS), eliminating the highly reactive superoxide radical and forming H2O2, which is then degraded by CAT, GPX, PRX and PRDX. SOD1 (CuZn-SOD) is a homodimer in the cytoplasm that is identified by its two polypeptide chains, whereas (Mn-SOD) (SOD_2) is a manganese-dependent tetramer situated in the mitochondria. (Zelko, et al., 2002; Surai, 2006; Cerchiaro, *et al.* 2022). EC-SOD levels were found to be lower and in reverse associated to BMI and HOMA-IR in a study of T2D patients(Bizoń, *et al.* 2022). Figure (1-6) is showing the sequencing reaction for the production and dissociation the hydrogen peroxide (Hayyan, *et al.* 2016).

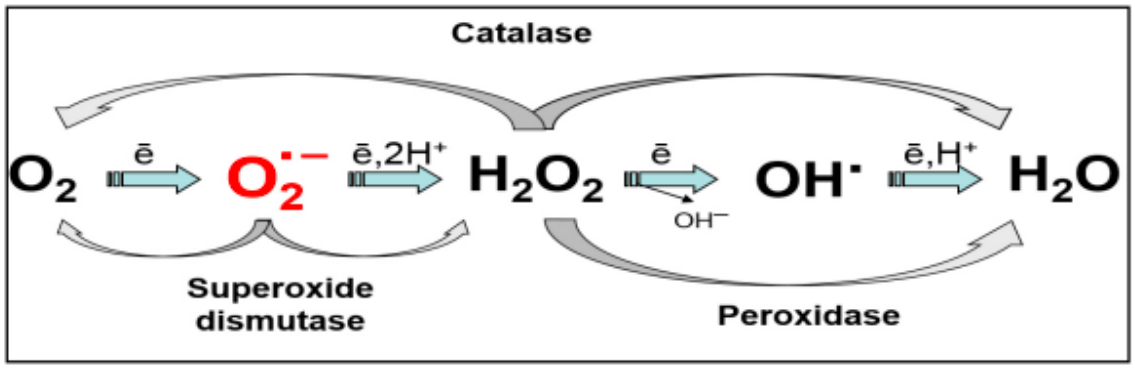


Figure (1-6): The mechanism of the peroxide formation

2. Catalase (CAT)

is an antioxidant enzyme situated in the peroxisomes is an extremely important antioxidant enzyme in the cell. Any hydrogen peroxide that surpasses physiological amounts is degraded. In obese mice, CAT expression was enhanced after calorie restriction (Rupérez, *et al.* 2014). In children with IR and obesity, its erythrocyte activity was decreased,

$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$ (Rupérez .A.,et al. 2014).

3. Glutathione peroxidase (GPX)

One of the major antioxidant defence systems in the body, the GPX family contains at least six isoenzymes, all of which are involved in the detoxification of hydrogen peroxide (Gupta, *et al.* 2019). Studies demonstrate that in the AT of obese rats, cellular and extracellular glutathione peroxidase (GPX) activity is reduced.

$2GSH + H_2O_2 \rightarrow GS–SG + 2H_2O$ (Fernandes, A., 2010).

4. Glutathione reductase (GR)

is found in the cytosol and mitochondria of cells and can catalyse the reaction of hydrogen peroxide to yield water and oxygen (Racchi, 2013) . Under normal conditions, glutathione is found throughout the body and is a major part of glutathione metabolism, (Erat, *et al*., 2007).

$$GSSG + NADPH + H^{+} \xrightleftharpoons{GR} 2GSH + NADP^{+}$$

1.9.2. Non – Enzymatic Antioxidants:

Free radical scavengers transform free radicals to a non-radical nontoxic form in non-enzymatic reactions. Most free radical scavengers are antioxidant compounds that balance a free radical by donating a hydrogen atom to the radical. Antioxidants therefore lower free radicals and are themselves oxidized in the reaction. Dietary free radical scavengers (e.g. vitamin E, ascorbic acid, carotenoids, and flavonoids) as well as endogenously created free radical scavengers (e.g., urate and melation) have a general structural advantage a conjugated double bond system that may be an aromatic ring (Smith. *et al.* 2006).

1.10. Malondialdehyde

Malondialdehyde (MDA) is a natural product formed in all cells as product of lipid peroxidation so it is most frequently used as indicators of lipid peroxidation. Reactive oxygen species (ROS) degrade polyunsaturated lipids, forming malondialdehyde. This compound is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells and form advanced glycation products. An elevated level of aldehyde is used as a biomarker to measure the level of oxidative stress in an organism. During oxidative damage, reactive lipid peroxidation products can form adducts with free amino groups of lysine and other amino acids in figure1-7.

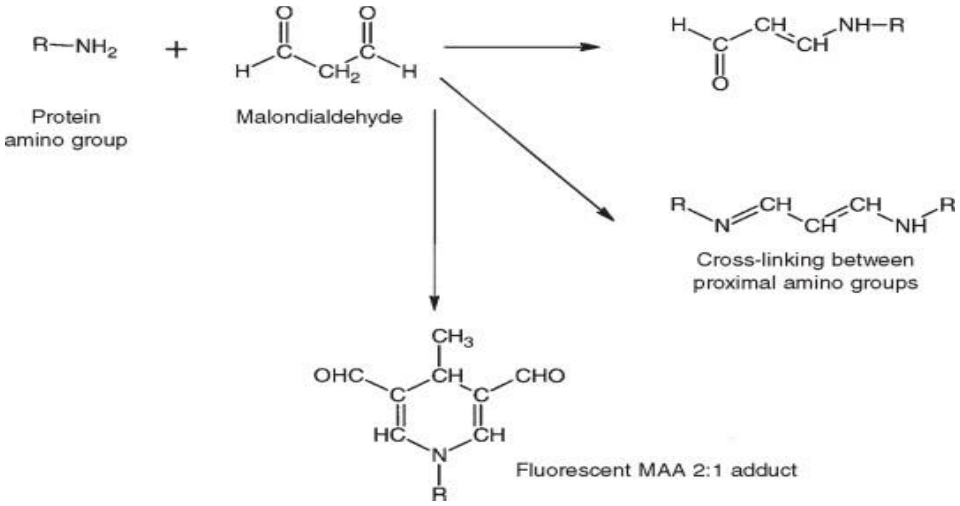


Figure 1-7 Structure of Malondialdehyde (Palacio, *et al*., 2006)

MDA is toxic and has been implicated in aging mutagenesis, carcinogenesis, diabetic nephropathy and radiation damage. Increased expression of MDA has been reported in the brains of Alzheimer's patients (Nair, *et al*. 2001;; Hadwan, 2008).

Aims of the Study

The study aims to:

1. Detection the role of obesity related parameters on the levels of Anti-inflammatory cytokine (Adiponectin and Adiponectin receptor1) in the diabetic obese patients compared with control group.

2. Calculate the Pro-inflammatory protein (Monocyte chemoattractant protein-1 MCP-1, Plasminogen Activator Inhibitor-1 PAI-1) in the diabetic obese patients compared with control group.

3. Calculate the hormone (FSH, LH) in the diabetic obese patients compared with control group.

4. Calculate the serum concentration of MDA, TAC, and TOS in the diabetic obese patients and to explore the correlation of them with biochemical parameters study(Adiponectin , Adiponectin receptor1, MCP-1 and PAI-1) depended on the fallowing variable obese patient woman with diabetes mellitus type two

5. Explore the correlation patient obese of ADIPO,ADIPOR1,MCP-1 and PAI-1 with patient non obesity

2. Materials and Methods

2.1. Materials

2.1.1. Chemicals and Kits

The chemicals and kits in the present study are used as supplied from purchases without additional purification. Kits and chemicals used in the present study are shown in Table 2-1.

Table 2-1 The Chemicals and Kit

Chemicals and Kits	Formula or Symbol	Purity %	Company and/or Country
Ferrous ammonium sulphate	$Fe(NH_4)_2(SO4)$	99%	BDH
Human Adiponectin ELISA Kit	ADIPO		Bioassay(china)
Human Adiponectin receptor ELISA Kit	ADIPO R1		Bioassay(china)
Human Plasminogen activation inhibitor-1 ELISA Kit	PAI-1		Bioassay(china)
Human Monocyte Chemoattractant Protein -1/ Monocyte Chemoattractic and Activating Factor ELISA Kit	MCP-1/CCL2/MCAF		Bioassay(china)
Ammoium acetate	$NH_4CH_3CO_2$	99.9%	Flluka
Thiobarbutiric Acid	$C_4H_4N_2O_2S$	98%	Fluka
Trichloroacetic Acid	$C_2HCl_3O_2$	98%	Fluka
Copper(II) chloride solution	$CuCl_2.2H_2O$	98%	Fluka
Sulphuric Acid	H_2SO_4	99%	Fluka
Ethanol	C_2H_6O	99.98%	Fluka
Sodium hydroxide	NaOH	99%	Gmbh
Total Cholesterol (TC) Kit	T.C		Human(Germany)

HDL-Cholesterol kit	HDL		Human(Germany)
Triglycerides (TGs) Kit	TG		Human(Germany)
Glucose kit	FBG		Human(Germany)
Human FSH ELISA Kit	FSH		Human(Germany)
Human LH ELISA Kit	LH		Human(Germany)
Sodium chloride	NaCl	99%	Sigma-Aldrich Inc
Gylcerol	$C_3H_8O_3$	99%	Sigma-Aldrich Inc
Hydrogen peroxide	H_2O_2	99%	Sigma-Aldrich Inc
o-Dianisidine dihydrochlorid	$C_{14}H_{16}N_2O_2 \cdot 2HCl$	99%	Sigma-Aldrich Inc**.**
Xylenol	$(CH_3)_2C_6H_3OH)$	99%	Sigma-Aldrich Inc**.**
Neocuproine (2,9-Dimethyl-1,10-phenanthroline)	$C_{14}H_{12}N_2$	99.9%	Sigma-Aldrich Inc**.**

2.1. 2. Instruments and Equipments

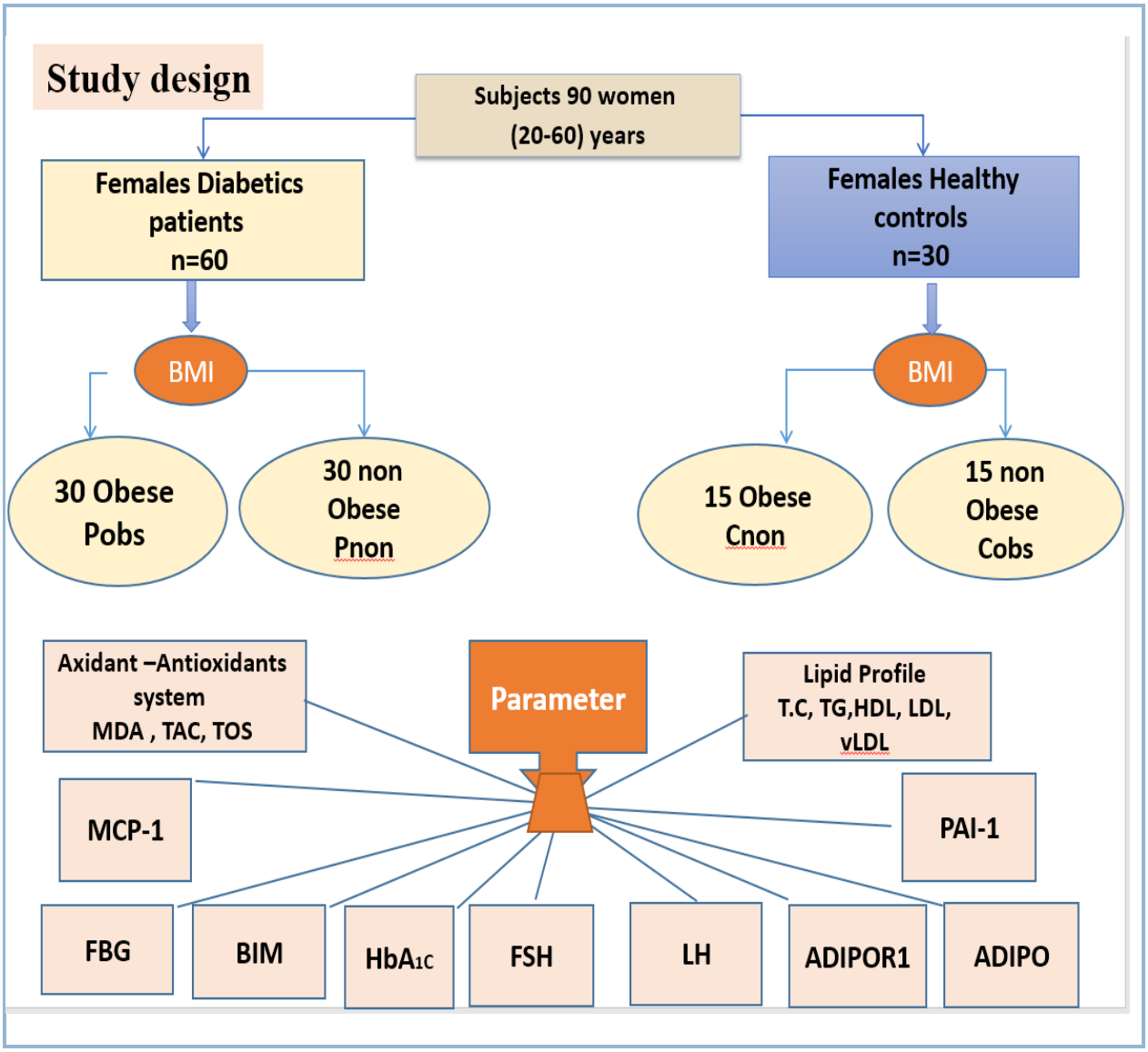
All instruments and tools which have been used in this study are listed in Table 2-2.

Table 2-2: Instruments and Equipments.

Instruments	Company and/or Country
Senstitive balance	Stanton 461
Vortex mixter	KAREL KOLB
Water bath	GFL
Centrifuge	Hermle labortechnik
Oven	Memmert
Micropipette 100-1000µL	RAGON MED
Micropipette 10-100µL	RAGON MED
UV-visible spectrophotometer UV-1100	EMCLPG T80(Germany)
Micro plate reader	Bio Tek(USA)

2.2. Subject

2.2.1. Study design



The study is case control study done carried out the Center for Diabetes and Endocrinology of Hilla city, Babylon, Iraq. Included in the following criteria is both patients and healthy people: The age (20 to 60) years of type 2 DM who visited diabetes centers during the study period from October to December 2021 and explain the graphical abstract in figure 2-1 .

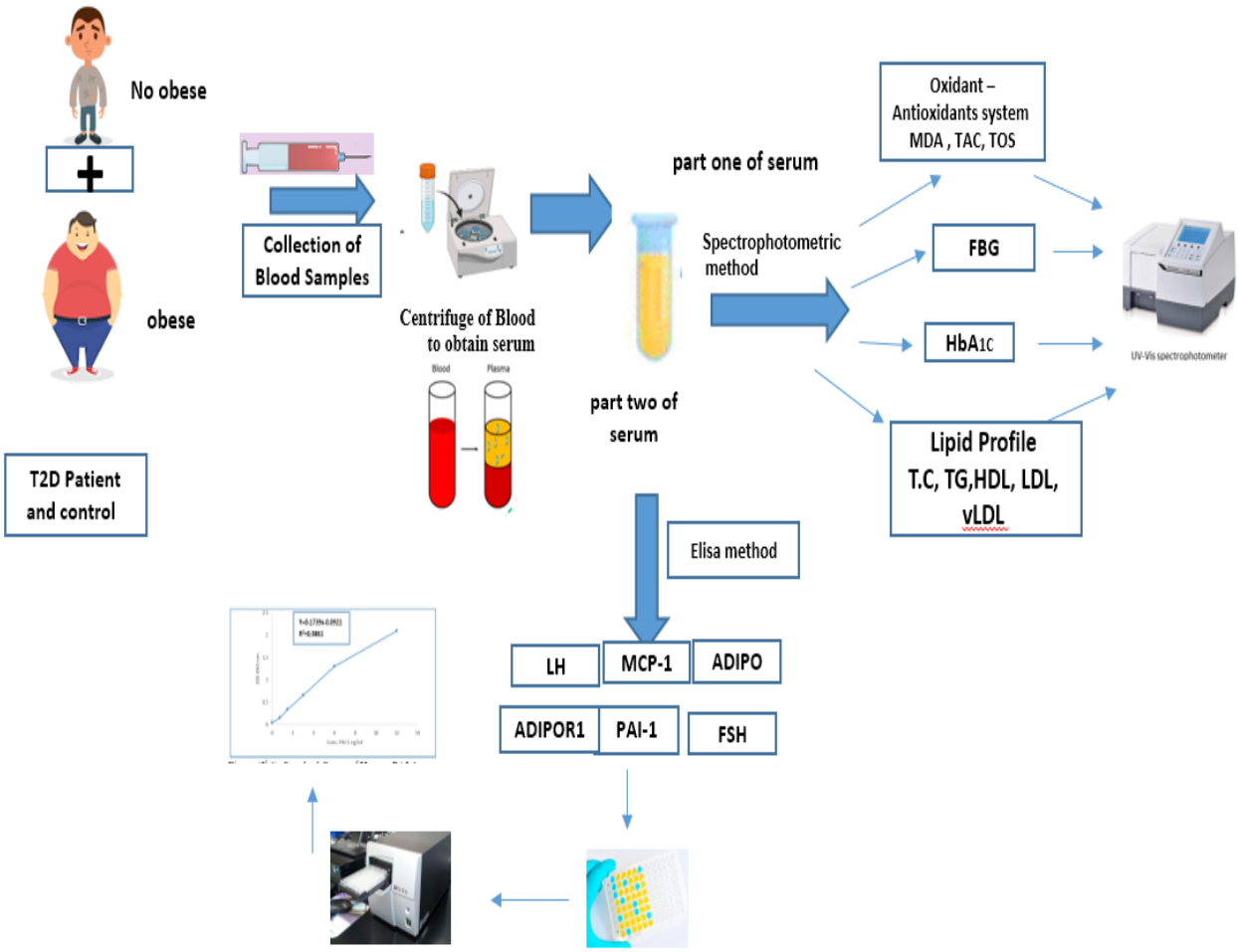


Figure 2-1 The Graphical Abstract of Subject

2.2.1.1 Patient Group (P)

Patient group involved (sixty) patients they were diagnosed with T2DM and divided in two group

30 women patients' obese (Po)

30 women patients non obese (Pnon)

With a mean age of All patients (20-60) years, were diagnosed by physicians and according to American Diabetes Association (ADA) urinating often, feeling very thirsty, feeling very hungry, extreme fatigue, blurry vision, cuts/bruises that are slow to heal, tingling, pain, or numbness in the hands/feet (type 2).

2.2.1.2 Control Group (C)

The Control healthy group involves (30) healthy subjects. Not all subjects appear any signs and symptoms of diseases. Controls subjects consist of

15 women obese (Co)

15 women non obese (Cnon)

were matched with patients in sex to increase the accuracy of the results. The blood samples were collected from relatives and medical staff of Marjan Teaching Hospital. Any patient with the following problems was excluded from the current study: a) heart diseases and hypertension. b) Insulin drug dependency. c) chronic liver disease. d) Smokers, Pregnant. e) Type 1 diabetic.

2.3. Methods

2.3.1 Collection of of Samples

The blood samples were drawn from fasting patients and control subjects. Five ml of blood were drawn from each participant by vein puncture, one ml was placed into EDTA-tubes and the residual 4 ml was put slowly into disposable tubes. Blood in the EDTA tubes was stored in - 20˚C in order to be used later in genetic part of the study, while blood in the gel containing tubes was centrifuged at 2000 × g for approximately 10-15 minutes then the sera were obtained stored at -20˚C until analysis

2.3.2. Body Mass Index (BMI)

Body mass index was calculated in all subjects according to ratio depend on weight and height obtained by applying a mathematical equation, in which the weight in kilogram is divided by the square height in meter, and the results were considered as follows :

BMI (kg/m^2) = weight (kg) / height (m^2) (Zhou et al. 2017)

Underweight ≤ 18.5(kg/m^2)

Normal weight between 18.5 - 24.9(kg/m^2)

Overweight between 25-29.9(kg/m^2)

Obese ≥30(kg/m^2) .

2.3.3. Inclusion and Exclusion Criteria of the current Study

The medical history of each patient was taken which included family history, type of treatment, duration of disease, and history of any other illness have in the patients who have essential in this study. Measurements of length and weight were done to calculate body mass index, the inclusion criteria were clinical T2DM and/or obese. At least controls were selected from apparently healthy adult volunteers with established levels of FBS S<100 mg/dl. Informed written consent was taken from each participant. Initially, all subjects were interviewed for their medical history and were examined. Both in cases and controls, exclusion criteria were set as having: history of cigarette smoking, history of heart failure, an account of malignancy, liver disease, and use of, insulin, lipid lowering drugs and antioxidants.

2.4. Biochemical Measurement

2.4.1. Glycated hemoglobin HbA_{1c}

2.4.1.1. Principal

This method directly determinates the hemoglobin A1c (HbA1c) in whole blood, using an antigen and antibody reaction. Total hemoglobin and HbA1c compite for the unspecific absortion rate to the latex particles (R1). Mouse anit-human HbA1c monoclonal antibody (R2a) binds to the coated particles with

HbA1c. The presence of goat anti-mouse IgG polyclonal antibody (R2b) causes the agglutination of the particles (complexes).The amount of agglutination is proportional to the concentration of the HbA1c in the sample and can be measured by turbidimetry.

2.4.1.2. Reagent

1. R1 Latex Suspension. polystyrene particles in a buffer, sodium azide 0.9 g/L, pH 8.0-8.3
2. R2a Antibody A. Mouse anti-human HbA1c monoclonal antibody in a buffer, sodium azide 0.9 g/L.
3. R2b Antibody B. Goat anti-mouse IgG polyclonal antibody in a buffer, sodium azide 0.9 g/L.

2.4.1.3. Procedure

1. The reagents and the photometer (cuvette holder) was Prewarm to 37ºC

2. Distilled water was used a blank in instrument at 660 nm.

3. Pipette into a cuvette reagent R1 750 µL, water (blank) 20 µL and all tube was Incubate 2 minutes at 37ºC.

4. Reagent R2a 250 µL was added and incubate 5 minutes at 37ºC.

5. Reagent R2b 125 µL was added.

6. The well was mixed and incubate at 37ºC for exactly 2 minutes. At the end of this period, read the absorbance (A) at 660 nm.

2.4.1.4. Calculation

The absorbance values (A) obtained was plotted against the HbA1c concentration of each calibrator. HbA1c concentration in the sample is

calculated by interpolation of its value (A) in the calibration curve. The assay is standardized according to the IFCC (International Federation of Clinical Chemistry) reference method, Although results may be calculated against DCCT (Diabetes Control and Complications Trial Research Group) method using the following formulas:

HbA1c IFCC (mmol/mol) = [HbA1c (NGSP) – 2.15] / 0.0915

HbA1c IFCC (%) = HbA1c (mmol/mol) IFCC / 10

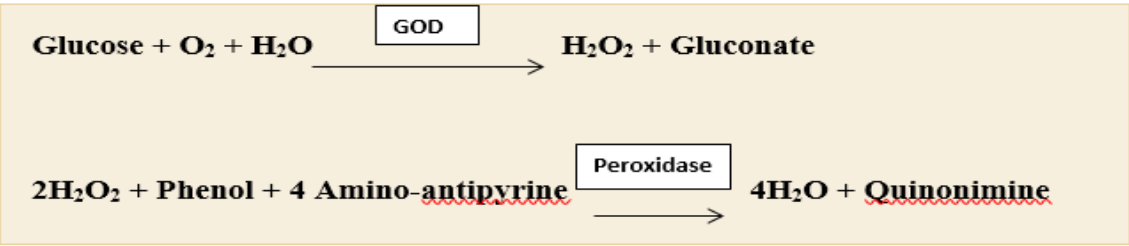
Measurement range. 1.5 % - 15.0 %

2.4.2. Determination of Fasting Blood Glucose (FBG) Concentration

The colorimetric method for quantitative in vitro diagnostic measurement using the Glucose kit was being used to assess the fasting serum glucose.

2.4.2.1. Principle

Glucose is oxidized by glucose-oxidase (GOD) to gluconate and hydrogene peroxide according to the following equation(Barham and Trinder, 1972) :



2.4.2.2 Reagents

1- Reagent 1 (Buffer):- Consist of 100 mmol/L of phosphate buffer pH7.5 and 0.75 mmol/L Phenol.

2-Reagent 2 (Enzymes):- Consist of ≥15 KU/L of glucose oxidase, ≥1.5 KU/L of peroxidase and 0.25mmol/L of 4-amino-antipyrine.

3- Reagent 3 (Standard):- Consist of 100 mg/dl or 5.55 mmol/L of glucose.

2.4.2.3. Preparation of Reagents

Working reagents are prepared by adding the substance containing reagent 2 in the vial (enzymes) to the vial of reagent 1 containing reagent 2 in the vial (Buffer). To complete the dissolving of all components, the mixture is mixed gently. The following table describes the procedure in table 2-3.

Table 2-3 The details of the FBG Concentration.

Reagent	Blank	Standard	Sample
Working reagent	1mL	1mL	1mL
Standard(STD)	----------	0.01mL	----------
Sample	----------	----------	0.01mL

The tube was putted in stand at a temperature (37 ºC) for five minutes after addition, then the absorbance was read at 500 nm.

2.4.2.4. Calculation

$$\textbf{Glucose (mg/L)} = \frac{\textbf{A.test}}{\textbf{A. STD}} * \textbf{Conc . of STD (100 mg/dl)}$$

Reference Values concentration between 75-115 mg/dl.

2.5. Determination Oxidant /Antioxidant System

2.5.1. Determination of Malondialdehyde

2.5.1. 1.Principle

The concept of this procedure was based on spectrophotometric measurement of the color, happen through the reaction between thiobarbituric acid and malondialdehyde (MDA) Figure 2-2 (Karim, *et al.* 2011) .

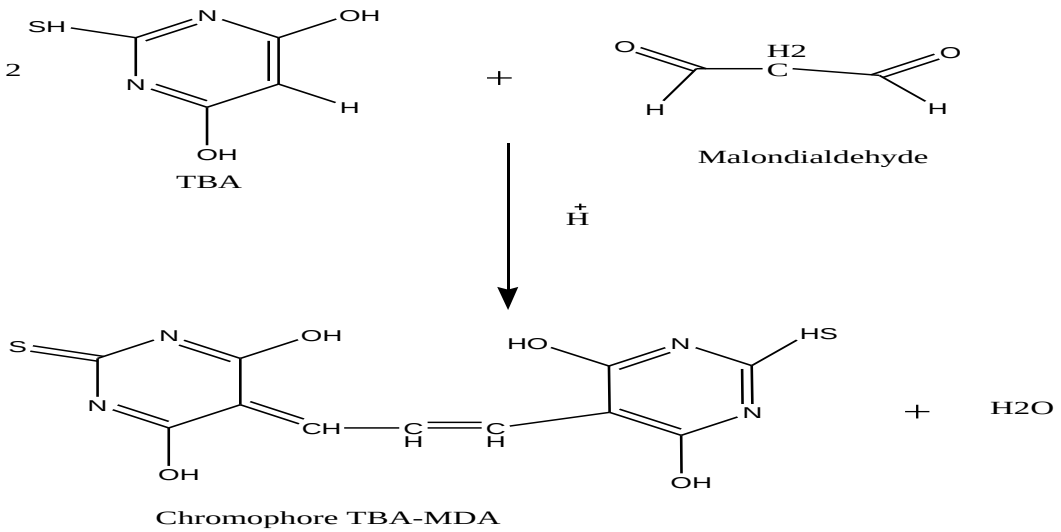


Fig. 2-2:-

Reaction between MAD and TBA Acid.

2.5.1. 2.Reagents:

1- TBA 0.6 % was prepared by dissolving 0.6 g of thiobarbutiric acid in 100 mL D.W.

2- TCA 17.5% was prepared by dissolving 17.5 g of trichloroacetic acid in 100 mL D.W.

3- TCA 70 % was prepared by dissolving 70 g of trichloroacetic acid in 100 mL D.W.

2.5.1.3.Procedure

Two tubes, represented sample and blank as follows.

Table 2-4 The details of the MAD method.

Reagents	Sample	Blank
Sample	150 µL	……
TCA (17.5 %)	1 mL	1 mL
TBA (0.6 %)	1 mL	1 mL
All tubes were mixed by vortex, incubated in boiling water bath (80 °C) for 15 minutes and then left to cool (at 25°C)		
TCA (70%)	1 mL	1 mL
D.D.W	……	150 µL

The solution was allowed to stand at room temperature for 20 minutes and centrifuged at 450 Xg for 15 minutes. The absorbance of all tubes was measured clear supernatant at 532 nm using spectronic 21 D.

2.5.1.4.Calculation:

The concentration of MDA μmole/ L = (A_{sample}/L *ε) * D

Where

L = light path (1cm)

ε = Molar extinction coefficient (1.56 *10^5 M^{-1} cm^{-1})

D = Dilution factor

D = 1ml (volume used in reference)/0.15ml (volume used in sample) = 1/0.15= 6.7

2.5.2.Total Antioxidants Capacity Assay: The CUPRAC Method.

2.5.2.1.Principle

Antioxidant + Cu^{2+} ⟶ Cu^{+}

Cu^{+} + 2.9-dimethyl-1,10-phenanthroline ⟶ complex (at 450 nm) (Apak., *et al.* 2005). (λ max at 450 nm).

2.5.2.2. Reagent

1- Copper (II) chloride solution at a concentration of 10^{-2} M was prepared from $CuCl_2$.$2H_2O$ weighing 0.4262 g, dissolving in H_2O and diluting to 250 ml with water.

2- Ammonium acetate (NH_4Ac) buffer pH=7.0 was prepared by dissolving 19.27 g of NH_4Ac in water and completed the volume to 250 ml.

3- Neocuproine (Nc) (2.9-dimethyl-1,1-phenanthroline) solution at concentration of 7.5 * 10^{-3} M was prepared by dissolving 0.04 g Nc in 96% EtOH,the volume was completed to 25 ml with ethanol .

4- The standard Uric acid solution (1mM) was prepared by dissolving 16.81 mg of uric acid in 100 ml of distilled water. To completely dissolve the Uric acid, some drops of sodium hydroxide are added to it.

2.5.2.3.Procedure

Table 2-5 The details of the CUPRAC Method.

Reagent	Test	STD	Blank
Copper (II) chloride solution	1mL	1mL	1mL
Sample	50µL	_____	_____
Working standard solution	_____	50µL	_____
D.W	_____	_____	50µL
Neocuproine (Nc) solution	1mL	1mL	1mL
Ammonium acetate (NH_4Ac) buffer	1mL	1mL	1mL
Test tubes was mixed by vortex and incubated for 30 minutes at 37 ºC and centrifuged at 4500 Xg for 2 minute, after that the absorbance was read on a spectrophotometer at 450 nm.			

2.5.2.3. Calculation

Total antioxidants levels= $\frac{A.test}{A.\ STD} * Conc.of\ STD\ (m\frac{mol}{L})$

2.5.3. Determination of Total Oxidant Status (TOS)

2.5.3.1. Principle

The TOS of serum was measured using a method, developed by Erel. Oxidants existing in the serum oxidize the ferrous ion–o-dianisidine complex to ferric ion. The oxidation reaction is improved by glycerol molecules, which are

abundantly found in the reaction medium. The ferric ion creates a colored complex with xylenol orange in an acidic medium. The color intensity, which can be determined spectrophotometrically, is associated with the total amount of oxidant molecules existing in the sample. The assay is calibrated with hydrogen peroxide and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (µmol H_2O_2 Eq/L) (Erel., 2005).

2.5.3.2. Reagents

Reagent 1 : It was prepared by dissolving 1.96 g of ferrous ammonium sulfate and 3.17 g od O-dianisidine dihydrochloride on 100 ml of H_2SO_4 solution ,25mM. The final reagent was consist of 5mM ferrous ammonium sulfate and 10 mM O-dianisidine dihydrochloride.

Reagent 2:It was prepared by dissolving 114 mg of xylenol orange and 8.18 g of NaCl in 900 ml of 25 mM H_2SO_4 solution. One hundred milliliters of glycerol was added to the solution. The final reagent was composed of 150µM xylenol orange ,140mM NaCl and 1.35 M glycerol. The pH value of the reagent was 1.7 . This reagent stable for at least 6 months at 4ºC.

Hydrogen peroxide (STD) : (100µmol/L) was freshly diluted and standardization daily using a molar extinction coefficient of 43.6M^{-1} cm^{-1} at 240 nm .

2.5.3.3. Procedure

Table 2-6 The Details of the Present TOS Method.

Reagent	Blank	STD	Test
D.w	25µL	_____	_____
Serum	_____	_____	25µL
Hydrogen peroxide	_____	25µL	_____
R_1	1mL	1Ml	1mL
Test tubes were mixed by vortex, then added:			
R_2	0.25mL	0.25mL	0.25mL
Test tubes were gently mixed and let to stand at room temperature for 30 minute, Absorption was read at 560 nm			

2.5.3.3. Calculation

Total oxidants levels= $\frac{A.test}{A.\ STD} * Conc\ .of\ STD\ (\mu\frac{mol}{L})$

2.6. Determination of Lipid Profile Levels

2.6.1. Determination of Serum Total Cholesterol

The total Serum cholesterol determined by the colorimetric method for the quantitative *in vitro* diagnostic measurement using a kit (*Perk, et al.*, 2012).

2.6.1.1. Principle

This method is for the measurement of the total serum cholesterol, which involves the use of three enzymes: cholesterol esterase (CE), cholesterol oxidase (CO) and peroxidase (POD). In the presence of the former, the mixture of phenol

and 4-aminoantipyrine (4AA) is condensed by hydrogen peroxide to form Quinoneimine dye proportional to the concentration of cholesterol in the sample.

The Serum cholesterol is measured using the enzymatic method based on the following reactions:

$$\text{Cholesterol ester} + H_2O \xrightarrow{CE} \text{Cholesterol} + \text{Free Fatty acids}$$

$$\text{Cholesterol} + O_2 \xrightarrow{CO} \text{Cholestene-3-one} + H_2O_2$$

$$2H_2O_2 + \text{phenol} + \text{4-amino-antipyrine} \xrightarrow{POD} \text{Quinoneimine (pink)} + 4H_2O$$

CE = Cholesterol esterase, CO = Cholesterol oxidase ,POD = Peroxidase

2.6.1. 2.Reagents

Table 2-7 The Details of the Total Cholesterol Regent.

Reagent	Content	Concentration
Reagent 1 Buffer	Phosphate buffer pH(6.5) Phenol	30 mmol/L 5 mmol/L
Reagent 2 Enzymes	4-amino-antipyrine Cholesterol Esterase Cholesterol Oxidase Peroxidase	0.3 mmol/L ≥ 150 U/L ≥ 100 U/L ≥ 5 KU/L
Reagent 3 Standard	Cholesterol	200 mg/dl

2.6.1.3. Procedure

The procedure for this method as the following: -

Table 2-8 The details of preparation of Total Cholesterol method

Reagent	Blank	Standard	Sample
Working reagent	1mL	1mL	1mL
Standard(STD)	----------	10 µL	----------
Sample	----------	----------	10 µL

All test tubes were mixed and permitted at 37 ºC for 5 minutes, and read absorbance by spectrophotometer at 500 nm.

2.6.1.4. Calculation

The total cholesterol (mg/dl) = Abs.of sample /Abs.of standard × Conc. St (200 mg/dl)

• Reference Values

The total cholesterol concentration in serum is <200 mg/dl.

2.6.2. Determination of serum Triglycerides (TGs)

Serum triglycerides were determined by the colorimetric method for the quantitative *in vitro* diagnostic measurement using a kit (Schettler, and Nussel, 1975).

2.6.2.1. Principle

The method is based on the enzymatic hydrolysis of serum or plasma triglyceride to glycerol and free fatty acids (FFA) by lipoprotein lipase (LPL). The glycerol is phosphorylated by adenosine triphosphate (ATP) in the presence of glycerol kinase (GK) to form glycerol-3-phosphate (G-3-P) and adenosine diphosphate (ADP) glycerol-3-phosphate is oxidized by glycerol-phosphate oxidase (GPO) to form dihydroxy acetone phosphate (DHAP) and hydrogen peroxide (Kalia, 2004).

A red chromogen is produced by peroxidase (POD) catalyzed coupling of 4-aminoantipyrine (4-AA) and phenol with hydrogen peroxide (H_2O_2) proportional to the concentration of triacylglycerol in the sample. The Serum triacylglycerol is measured using an enzymatic method based on the following reactions:

$$\text{Triglycerides} \xrightarrow{\text{Lipase}} \text{Glycerol} + \text{free fatty acids}$$

$$\text{Glycerol} + \text{ATP} \xleftrightarrow{\text{GK}} \text{Glycerol 3 phosphate} + \text{ADP}$$

$$\text{Glycerol -3- phosphate} + O_2 \xleftrightarrow{\text{GDP}} \text{Dihydroxyacetone phosphate} + H_2O_2$$

$$H_2O_2 + \text{4-aminoantipyrine} \xrightarrow{\text{POD}} \text{Quinoneimine (pink)} + H_2O + HCl + \text{4- Chlorophenol}$$

GK = Glycerol Kinase , GPO = Glycerol-3-phosphate oxidase , POD = Peroxidase

The absorbance of the coloured complex (quinoneimine), proportional to the amount of TGs in the serum, is measured at 500 nm .

2.6.2.2. Reagents

Table 2-9 The Details of Preparation of Triglycerides Regent method.

Reagent	Content	Concentration
Reagent 1 Buffer	PIPES (pH7.5) Magnesium chloride 4- Chlorophenol	50 mmol/L 4.5 mmol/L 5mmol/L
Reagent 2 Enzymes	4-amino-antipyrine Lipases Glycerol Kinase(GK) Peroxidase (POD) Glycerol -3- phosphate oxidase (GPO) Adenosine triphosphate Na (ATP)	0.25 mmol/L ≥ 1300U/L ≥ 400U/L ≥ 5 KU/L ≥1500U/L 2mmol/L
Reagent 3 Standard	Triglyceride	200mg/dl

2.6.2.3. Procedure

Three sets of tubes (Sample, Standard, and Blank) are prepared as the following:

Table 2-10 The Details of the Triglycerides Method

Solutions	Blank	Standard	Sample
Working reagent	1 Ml	1 Ml	1 mL
Distilled water	10 µL	———	———
Standard	———	10 µL	
Serum	———	———	10 µL

Content of every tube was gently mixed and allowed to stand at room temperature for 10 minute or incubate at 37 ºC for 5 minute and read at 505 nm against reagent blank.

2.6.2.4 Calculation:

TG in (mg/dL) = A (Sample)/ A (Standard) x Standard conc. 200mg/dL

• Reference Values

TG concentration in serum is between 35- 160 mg/dl

2.6.3. Determination of High Density Lipoprotein-Cholesterol (HDL-C)

2.6.3.1. Principle:

Firstly, low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein-cholesterol (VLDL-C) and chylomicrons are precipitated from specimens by Phosphotungstic acid and $MgCl_2$. After centrifugating the specimens, it is found that supernatant contains HDL-C then treated as total cholesterol (Gordon, *et al*. 1977)

2.6.3.2. Reagents:

Table 2-11 The Details of the High Density Lipoprotein-Cholesterol Reagent

Reagents	Compounds	Concentration
Reagent 1 Buffer	Phosphotungstic acid Magnesium Chloride	0.55mmol/L 25mmol/L
Reagent 2 Standard	HDL- Cholesterol	50 mg/dl

2.6.3.3. Procedure

Three sets of tubes (Sample, Standard, and Blank) are arranged as the following in table 2-12

Table 2-12 The details of the High Density Lipoprotein-Cholesterol Method

Solutions	Blank	Standard	Sample
Working reagent	1 ml	1 ml	1 ml
Distilled water	100µl	———	———
Standard	———	100µl	
Supernatant	———	———	100µl

The working solution is the cholesterol enzymatic solution. Gently mix the content of every tube after addition, allow standing at room temperature for 10 minutes or incubating for 5 minutes at 37 º C and reading spectrophotome6trically at 500 nm against reagent blank.

2.5.3.4. Calculation

HDL-C (mg/dL)= A (Sample) / A (Standard) × Standard conc. (50mg/dL)

• Reference Values

HDL-C Concentration in serum is between 35-55mg/dl

2.6.4. Assessment of Very Low Density Lipoprotein- Cholesterol

2.6.4.1 Principle

Very low density lipoprotein- cholesterol (VLDL-C) is calculated by dividing the triglycerides concentration by 5 and it characterize the concentration in milligram per deciliter.

Low density lipoprotein- cholesterol(LDL-C) is calculate49-d by the indirect method(National Institutes of Health. ,2001). .

LDL-C= total cholesterol – (HDL-cholesterol + VLDL cholesterol).

LDL-C = total cholesterol - (HDL-cholesterol + TG/5)

• Reference Values

Normal value of LDL cholesterol less than 100 mg/dl

2.7. Determination of Adiponectin ADIPO Levels (mg/L)

2.7.1 Principle

This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate has been pre-coated with Human APM1 antibody. APM1 present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human APM1 Antibody is added and binds to APM1 in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated APM1 antibody. After incubation unbound Streptavidin-HRP is washed away during a washing step. Substrate solution is then added and color develops in proportion to the amount of Human

APM1. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

2.7.2 Reagents

1. Standard Solution: Consist of 1 vial contains 0.5ml of 160ng/ml Adiponectin
2. Standard Diluents: Consist of 1 vial contains 3ml of diluents.
3. Streptavidin –HRP Conjugate Reagent: Consist of 1 vial contains 6ml of HRP reagent.
4. Biotinylated Antibody: Consist of 1 vial contains 1ml of biotinylated antibody
5. Substrate Solution A: Consist of 1 vial contains 6ml of solution.
6. Substrate Solution B: Consist of 1 vial contains 6ml of stop solution.
7. Stop Solution: Consist of 1 vial contains 6ml of stop solution.
8. Wash Solution: Consist of 1 vial contains 20ml of wash solution.

2.7.3 Reagent Preparation

- **Standard Reconstitute** the standard was prepared by added 120µl of (64mg/L) with 120ul of standard diluent to generate a 32mg/L standard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare duplicate standard points by serially diluting the standard stock solution (32mg/L) 1:2 with standard diluent to produce 16mg/L, 8mg/L, 4mg/L and 2mg/L solutions.

- **Wash Buffer** was diluted by added 20ml of wash buffer concentrate 25x into deionized or distilled water to yield 500 ml of 1x Wash Buffer. If crystals have formed in the concentrate, mix gently until the crystals have completely dissolved.

2.7.4 Procedure

1- All reagents was prepared, standard solutions and samples as instructed. All reagents was put in room temperature before use.

2- The number of strips was determined required for the assay 2-8°C.

3- Fifty microliters of standard was added to standard well.

4- Forty microliters of sample was added to sample wells and 10µl Human APM1 antibody was added to sample wells, t

5- Fifty microliters of streptavidin-HRP was added to sample wells and standard wells (Not blank control well). The well was mixed, the plate was cover with a sealer. Incubate 60 minutes at 37°C.

6- The sealer was removed and the plate was washing 5 times with wash buffer.

7- Four hundred microliters was Soaked the wells for 30 seconds to 1 minute for each wash, 5 times with wash buffer. Blot the plate onto paper towels or other absorbent material.

8- Fifty microliters of substrate solution A was added to each well and 50ul substrate solution B was added to each well, the plate was covered with a new sealer for 10 minutes at 37°C in the dark.

9- Fifty microliters of Stop Solution was added to each well, color was changed from blue to yellow immediately.

10- The optical density (OD) value was determined of each well immediately using a microplate reader set to 450 nm within 10 minutes after adding the stop solution.

10- The absorption was read by used A microtiter plate reader at 450 nm

2.7.5 Calculation

A dose response standard curve is used to evaluate the concentration of adiponectin in serum as shown in figure 2-3.

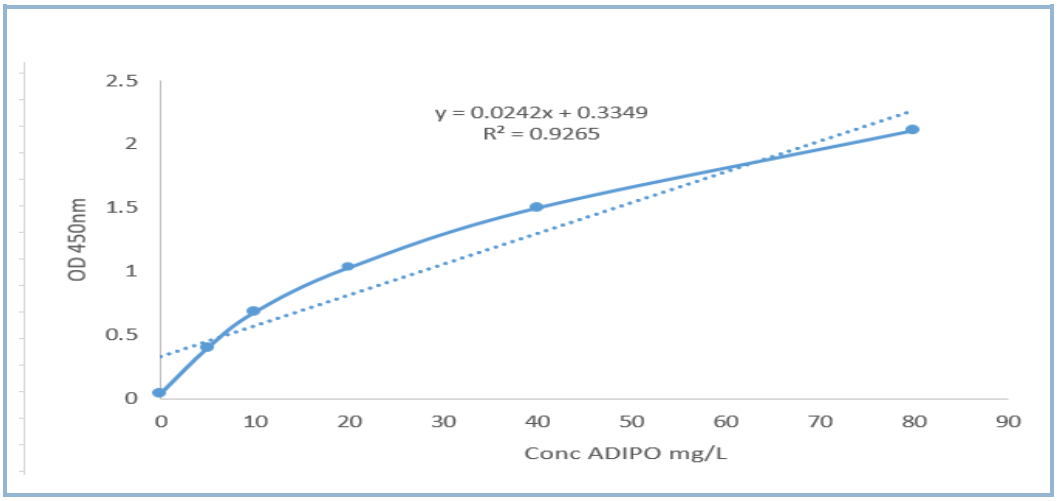


Figure 2-3 : Standard Curve of Human ADIPO

Standard Curve Range 0.2-60mg/L

2.8. Determination of Adiponectin Receptor Protein 1 (ADIPOR1) Concentration

2.81. Principle

Same in point 1.6.1

2.8.2 Reagents

1. Standard Solution: Consist of 1 vial contains 0.5ml of 160ng/ml Adiponectin Receptor Protein 1

2.Other reagent same point 2.6.3

2.8.3 Reagent Preparation

- **Standard Reconstitute** the 120µl of the standard (160ng/ml) with 120ul of standard diluent to generate a 80ng/mlstandard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare duplicate standard points by serially diluting the standard stock solution (80ng/ml) 1:2 with standard diluent to produce 40ng/ml, 20ng/ml,

10ng/ml and 5ng/ml solutions..This process was repeated to get the remaining standards as shown in figure 2-4 The total volume in all the wells is 120µl

Wash Buffer in point 2.6.3

2.8.4 Procedure

1. Found in point 2.6.4

2.8.5 Calculation

A dose response standard curve is used to evaluate the concentration of adiponectin Resptor1 in serum as shown in figure 2-4).

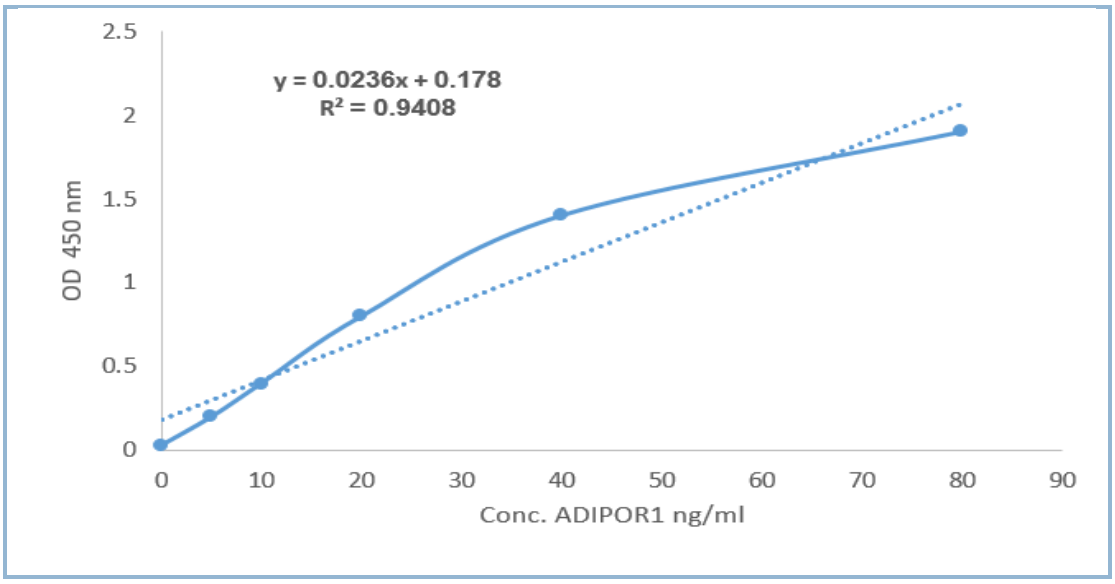


Figure 2-4 Standard Curve of Human ADIPOR1

Standard Curve Range 0.5-150ng/ml

2.9. Human Plasminogen Activator Inhibitor 1, PAI-1

2.9.1. Principle

Found in point 2.6.1

2.9.2 Reagents

Reagents preparation

1. Standard Solution: Consist of 1 vial contains 0.5ml of 160ng/ml SERPINE1
2. Other reagent found in point 2.6.2

2.9.3 Reagent Preparation

- **Standard Reconstitute** the 120µl of the standard (24ng/ml) with 120µl of standard diluent to generate a 12ng/mlstandard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare duplicate standard points by serially diluting the standard stock solution (12ng/ml) 1:2 with standard diluent to produce 6ng/ml, 3ng/ml, 1.5ng/ml and 0.75ng/ml solutions.

2. Wash Buffer Found in point 2.6.4

2.9.4. Procedure Found in point 2.6.4

2.9.5 Calculation

A dose response standard curve is used to evaluate the concentration of PAI-1 in serum as shown in figure 2-5.

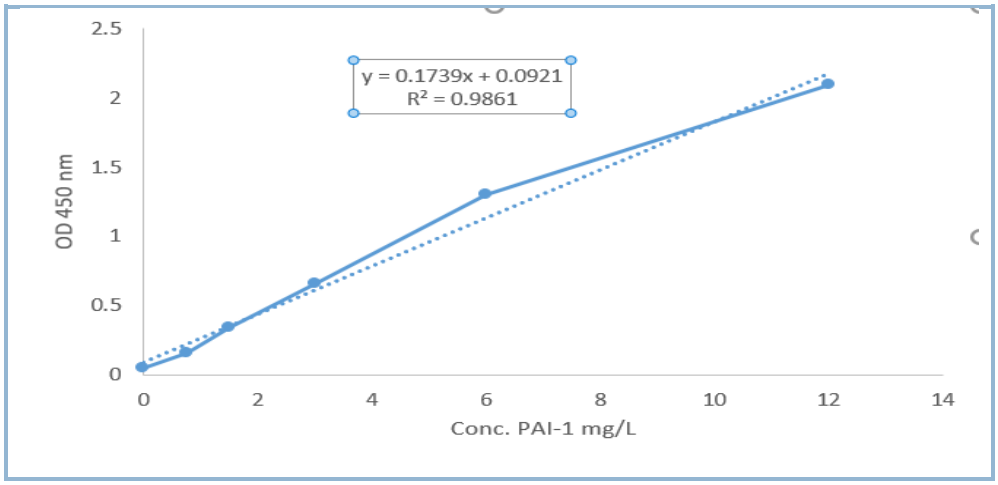


Figure 2-5 : Standard Curve of Human PAI-1

Standard Curve Range 0.05-20ng/ml

2.10. Determination of Monocyte Chemotactic Protein-1 MCP-1

2.10.1.Principle

Found in point 2.6.1

2.10.2 Reagents

Reagents preparation

2. Found in point 2.6.2

2.10.3 Reagent Preparation

1. Standards Preparation:

- **Standard Reconstitute** the 120nl of the standard (1920ng/L) with 120ul of standard diluent to generate a 32mg/Lstandard stock solution. Allow the standard to sit for 15 mins with gentle agitation prior to making dilutions. Prepare duplicate standard points by serially diluting the standard stock solution (960ng/L) 1:2 with standard diluent to produce 960 ng/L, 480ng/L,

240ng/L, 120ng/L and 60ng/L solutions. The total volume in all the wells is 120µl.

3. **Wash Buffer** Found in point 2.6.3

2.10.4 Procedure

Found in point 2.6.4

2.10.5 Calculation

A dose response standard curve is used to evaluate the concentration of MCP-1in serum as shown in Figure 2-6.

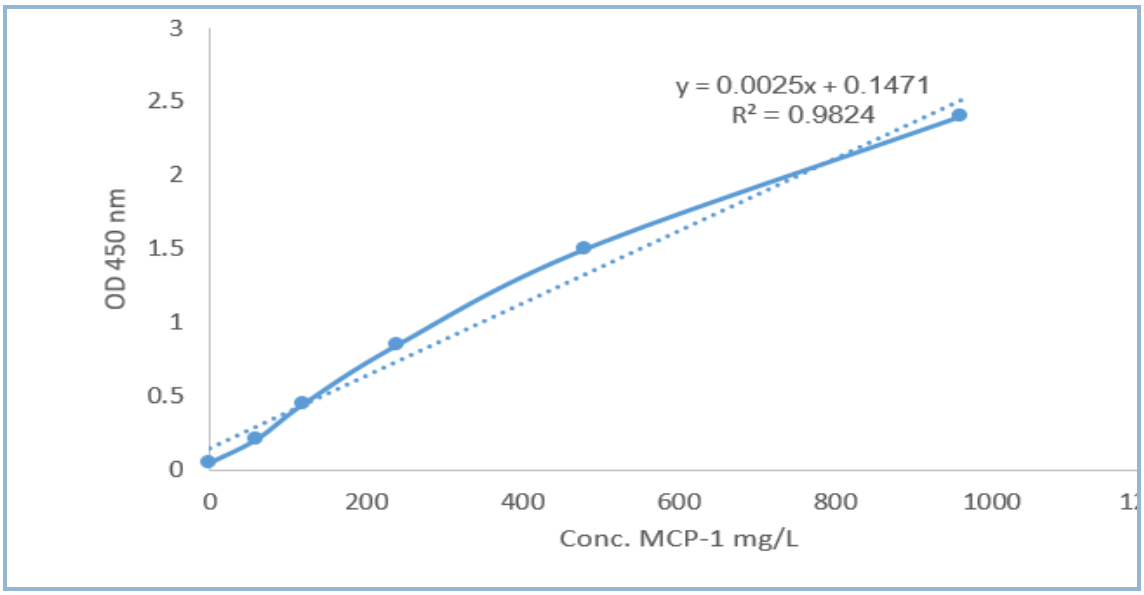


Figure 2-6: Standard Curve of Human MCP-1

Standard Curve Range 5ng/L-1500ng/L

2.11. Quantitative Determination of Follicle Stimulating Hormone (FSH)

2.11.1 Principle

The Human FSH ELISA is intended for professional use. The ELISA for direct antigen detection uses the high affinity of Biotin for Streptavidin, which has

been coated on the surface of microtiter wells. In the first incubation step, specimens, calibrators or controls and enzyme conjugate (peroxidase-labelled anti-FSH and biotinylated monoclonal anti-FSH) are mixed to form a specific immunocomplex which is bound to the surface of the wells by the interaction of biotin with the immobilised streptavidin. At the end of the incubation excess enzyme conjugate and monoclonal antibodies are washed out. TMB/Substrate is added (step 2) and the resulting colour, which turns into yellow after stopping the reaction with the stop solution, is measured photometrically. The intensity of colour is directly proportional to the FSH concentration in the sample. The absorbance of calibrators and specimen is determined by using ELISA microplate readers or automated ELISA systems (like HUMAN's HumaReader or ELISYS line). The concentration is evaluated by means of a calibration curve which is established from the calibrators supplied with the kit (Odell, *et al.* 1981**)**

2.11.2.Reagents

Reagents and Contents

1. [MIC] 12ml Microtiter Strips 8-well snap-off strips were coated with streptavidin.
2. [CAL] A - F Calibrators 6x2.0ml ready was used, in human serum, yellowish FSH level: 0 (A), 5 (B), 10 (C), 25 (D), 50 (E), and 100 (F) IU/l
3. [CON] 13 ml Enzyme Conjugate, coloured greenish-blue anti-FSH (monoclonal, mouse), HRP-labelled, anti-FSH (monoclonal, mouse), biotinylated 1.0 µg/ml.
4. [WS 50x] 20 ml Wash Solution (black cap) Concentrate for approx. 1000 ml Tris buffered saline 250 mmol/l
5. [SUB] 14 ml Substrate Reagent 3,3', 5,5'-tetramethylbenzidine (TMB) < 0.25 g/l Sodium acetate buffer 0.03 mol/l Hydrogen peroxide
6. [STOP] 7.5 ml Stop solution Sulphuric acid 0.5 mol/l 1 Adhesive strip

2.11.3. Procedure

Table (2-13) The details of the FSH procedure

Reagents and specimens should be at room temperature before use.		
step 1	Wel [µl]	
	Calibrators	Specimen
[CAL] A-F; in duplicate	50	…
Specimens, Controls; in duplicate		50
[CON]	100	100
Rock gently and cover [MIC] with Adhesive Strip Incubate 60 min at 20...25°C Wash 3 times as described (see W1 - W3)		
Step 2		
	100	100
Do not shake [MIC] after [SUB] addition Incubate 15 min at 20...25°C		
[STOP]	50	50
Mix carefully		
Measure the absorbance at 450 nm as soon as possible or within 30 min. after terminating of reaction, using a reference wavelength of 630-690 nm (if available).		

2.11.4.Reagent Preparation

The reagents were Bring to room temperature (25°C) before use. Reagents not in use should always be stored at 28°C.

Working Wash Solution

– The wash was Diluted to 1000 ml with fresh, deionised water in a suitable container. Rinse vial several times.

2.11.5 Calculation

The response standard curve is used to evaluate the concentration of FSH in serum as shown in figure 2-7.

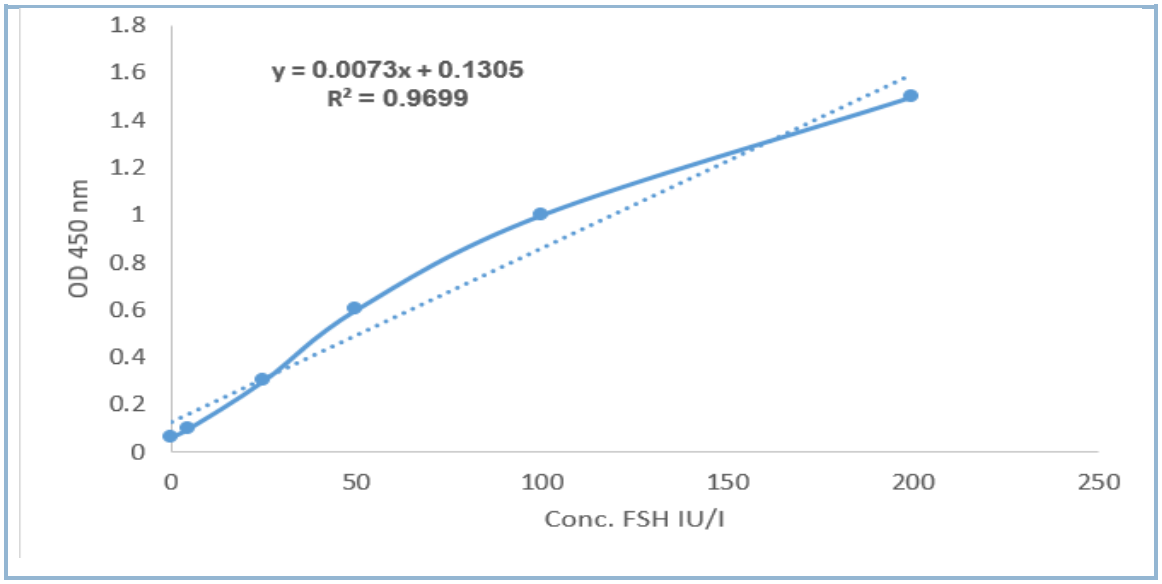


Figure 2-7 Standard Curve of Human FSH

Table 2-14 Expected Values for FSH Levels

Expected Values for FSH Levels throughout Normal Menstrual Cycle	
Cycle phase	**FSH [IU/l]**
Follicular phase	**3-12**
Postmenopausal	**35-151**

2.12. Quantitative Determination of Luteinizing Hormone (LH)

2.12.1 Principle

The ELISA for direct antigen detection uses the high affinity of Biotin for Streptavidin, which has been coated on the surface of microtiter wells. In the first incubation step, specimens, calibrators or controls and enzyme conjugate (peroxidase-labeled anti-LH and biotinylated monoclonal anti-LH) are mixed to form a specific immune complex which is bound to the surface of

the wells by the interaction of biotin with the immobilised streptavidin. At the end of the incubation excess enzyme conjugate and monoclonal antibodies are washed out. TMB/Substrate is added (step 2) and the resulting colour, which turns into yellow after stopping the reaction with the stop solution, is measured photometrically. The intensity of colour is directly proportional to the LH concentration in the sample (Goldstein, D., and Kosasa, T., 1975).

2.12.2. Reagents

1. [MIC] 12 Microtiter Strips was coated with streptavidin
2. [CAL] A - F Calibrators 6x2.0ml ready for use, in human serum, yellowish LH level: 0 (A), 5 (B), 25 (C), 50 (D), 100 (E), and 200 (F) IU/l
3. [CON] 13 ml Enzyme Conjugate was coloured orange anti-LH (monoclonal, mouse), HRP-labelled, anti-LH (monoclonal, mouse), biotinylated 1.0 µg/ml
4. [WS]50x] 20 ml Wash Solution ,1000 ml Tris buffered saline 250 mmol/l
5. [SUB] 14 ml Substrate Reagent ,3,3', 5,5'-tetramethylbenzidine (TMB) < 0.25 g/l Hydrogen peroxide Sodium acetate buffer 0.03 mol/l
6. [STOP 7.5 ml Stop solution (red cap) Sulphuric acid 0.5 mol/l 1 Adhesive strip Preservatives: Total concentration < 0.04%. Additional materials recommended but not supplied with the kit Micropipettes, ELISA washer, microplate reader equipped with 450 nm or with 450/630-690 nm filters, deionised water.

Table 2-15 The Details of LH Hormone

Reagents and specimens should be at room temperature before use.		
step 1	Wel [µl]	
	Calibrators	Specimen
[CAL] A-F; in duplicate	50	…
Specimens, Controls; in duplicate		50
[CON]	100	100
Rock gently and cover [MIC] with Adhesive Strip Incubate 60 min at 25°C Wash 3 times as described (see W1 - W3)		
Step 2		
	100	100
Do not shake [MIC] after [SUB] addition Incubate 15 min at 20...25°C		
STOP	50	50
Mix carefully		
Measure the absorbance at 450 nm as soon as possible or within 30 min. after terminating of reaction, using a reference wavelength of 630-690 nm (if available).		

2.12.3. Reagent Preparation

All reagents was put at room temperature (25°C) before use. Reagents not in use should always be stored at 28°C.

Working Wash Solution [WASH]

Same in FSH

2.12.4. Calculation

A dose response standard curve is used to evaluate the concentration of in serum LH as shown in Figure 2-8.

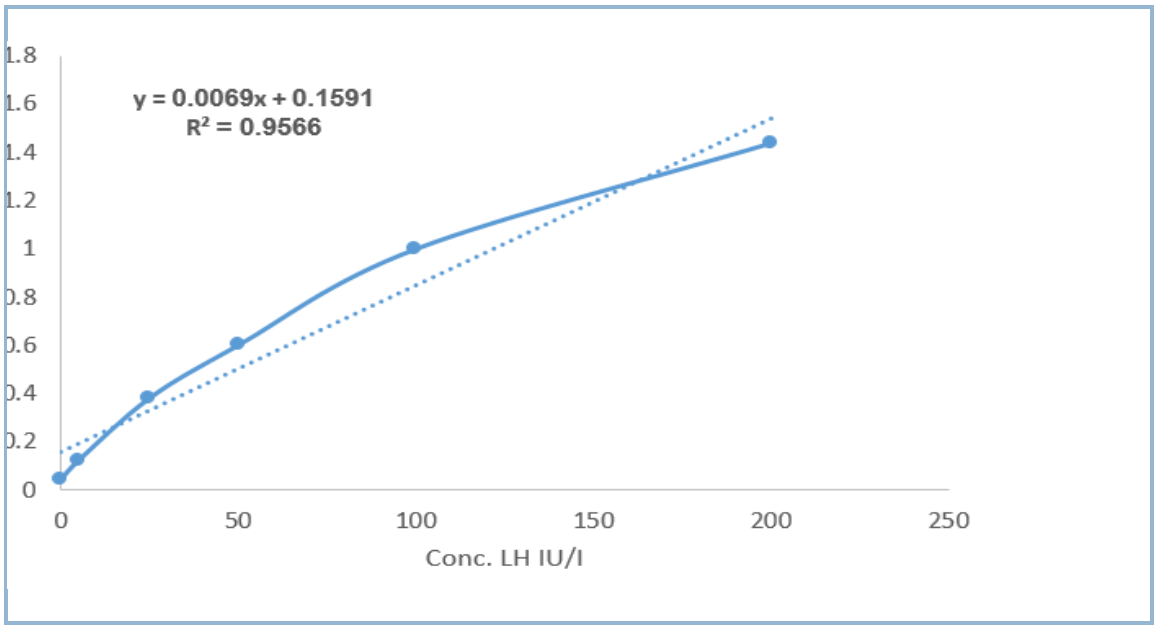


Figure 2-8 Standard Curve of Human LH

Table 2-16 Expected Values for LH Levels

Expected Values for LH Levels throughout Normal Menstrual Cycle	
Cycle phase	**LH [IU/l]**
Follicular phase	**0.8-10.5**
Postmenopausal	**8.2-40.8**

2.13. Statistical Analysis

Statistics from the SPSS version (V.26.0) were utilized for statistical analysis. The findings were analyzed using means, standard deviations, and ANOVA to determine the difference between groups. Students' assessments were compared to two average semesters. Pearson's correlation coefficients were used to compare the relationships between variables. The p values of test was two-tailed, and P values of 0.05 were considered significant.

3. Results and Discussion

3.1. Characteristics of Patients Group and Control Group

Table 3-1 demonstrates the base line characteristics of the study, which includes the data of patients group, and control group. It contains age, BMI, FBS, T.C, T.G, HDL-C, LDL-C, VLDL-C, duration of disease, duration of medication, FSH, LH, MCP-1, PAI-1, ADIPO, ADIPOR1, TCA, MAD, TOS.

Table 3-1 Criteria Clinical Measurements of the Samples Population (mean ± SD)

Parameters	Patients Mean+SD	Control Mean+SD	P -value
Age (years)	48.80±13.13	50.48±13.41	0.081
BMI(kg/m^2)	29.46 ±5.05	27.53±6.05	0.149
FBG(mg/dL)	187.15±67.51	80.25±12.92	0.00001
HbA1C%	9.34±1.27	5.17±0.79	0.00001
T.C(mg/dL)	266.71±62.13	130.07±30.08	0.00001
T.G(mg/dl)	253.52±100.64	118.35±23.66	0.00001
HDL-C(mg/dL)	44.23±7.13	50.98±9.16	0.00001
LDL-C (mg/dL)	171.77±55.94	55.41±32.81	0.00001
VLDL-C (mg/dL)	50.70±20.12	23.67±4.73	0.00001
Duration of disease (years)	5.39±2.69	_____	

Duration of medication (years)	4.83±2.17	_____	
FSH IU/l	5.62±1.99	7.16±2.76	0.002
LH IU/l	8.82±3.49	10.27±4.51	0.122
MCP-1 mg/L	214.60±141.91	85.58±15.10	0.00001
PAI-1 mg/L	5.14±2.53	2.11±1.55	0.00001
ADIPO mg/L	14.96±3.89	20.10±5.45	0.00001
ADIPOR1 ng/mL	16.30±4.49	22.37±3.28	0.00001
TAC mmol/L	0.69±0.25	0.86±0.43	0.021
MAD µmol /L	2.14±1.40	1.24±0.61	0.001
TOS µmol /L	1.02±0.48	0.97±0.38	0.627

A significant (P<0.001) elevation was found of the FBS, total cholesterol, T.G vLDL-C-, HDL-C, LDL-C, Duration of disease, Duration of medication, FSH, MCP-1, PAI-1, ADIPO, ADIPOR1, TAC and MAD in patients group while associated with the healthy group. On the other hand, nonsignificant variations were indicated in the data of the age, BMI, TOS and LH in the groups of patients with respect to the group of the control subjects.

When comparing patients with healthy subjects, we find two constant factors, age and BMI, because they are the same for all patients, and therefore give a result nonsignificant , Also, TOS LH is not affected by fracture, while the effect of obesity on them is more

3.2. Biochemical Studies

3.2.1 Measurement of BMI, FSB, HbA_{1C} in T2DM Patients and Control Subjects

Fasting serum glucose was measured in 30 T2DM obese individuals group, 30 non-obese patients group, 15 control obese healthy group and 15 control non obese healthy group.

Table 3-2 BMI, Fasting serum glucoseHbA$_{1C}$ and in the study subjects.

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
FBG	30	Po	172.71±63.15	149.13	196.29	Po	Pnon	0.046
							Co	0.00001
							Cnon	0.00001
	30	Pnon	201.59±69.66	175.57	227.60	Pnon	Co	0.00001
							Cnon	0.00001
	15	Co	81.22±15.52	70.69	87.88	Co	Cnon	0.924
	15	Cnon	81.10±10.14	75.60	86.84			
BMI	30	Po	33.54±3.31	32.30	34.78	Po	Pnon	0.00001
							Co	0.543
							Cnon	0.00001
	30	Pnon	25.37±2.53	24.42	26.32	Pnon	Co	0.00001
							Cnon	0.002
	15	Co	32.97±2.99	31.32	34.63	Co	Cnon	0.00001
	15	Cnon	22.42±2.82	20.85	23.98			
HbA$_{1C}$	30	Po	9.44 ± 1.38	8.93	9.96	Po	Pnon	0.470
							Co	0.00001
							Cnon	0.00001
	30	Pnon	9.23 ± 1.16	8.79	9.66	Pnon	Co	0.00001
							Cnon	0.00001
	15	Co	4.93± 0.75	4.51	5.35	Co	Cnon	0.253
	15	Cnon	5.41 ± 0.78	4.97	5.84			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese

As shown for patients and controls as illustrated in Table (3-2) . Obese patients have low FBG (172.71±63.15), high HbA_{1C} (9.44±1.38), with BMI(33.543.31±) compared to non obese patients FBG (201.59±69.66), HbA_{1C}(9.23 ± 1.16), with BMI(25.37±2.53), according to criteria compared to obese control FBS (81.22±15.52), HbA1C(4.93± 0.75), with BMI (32.97±2.99) compared another non obese control FBS(81.10±10.14), HbA1C(5.71 ± 0.78), with BMI (22.42±2.82).

High BMI is one of the risk factors associated with T2DM and the unhealthy factors that contribute to both obesity and T2DM where obesity was diagnosed when BMI measurements were used alone. T2DM patients who suffer from obesity leads to poor control blood sugar (Almubarak, ,2016 ;Sabanayagam, *et al* ,2021)

3.2.2. Oxidant –Antioxidant System

TOS levels TAC and, MDA were comparison between different groups for patients and controls as illustrated in Table (3-3). Obese patients have low TAC (0.56±0.21) with high MDA (2.95±1.52) and high TOS (1.23 ±0.52) compared to nonobese patients TAC (0.82±0.22) with MDA (1.33±0.55) and TOS (0.81±0.34), respectively compared to obese control TAC (0.64±0.14) with MDA (1.22±0.48) and TOS (1.11±0.45) compared another nonobese control TAC (1.08±0.50) with MDA (1.22±0.48) and TOS (0.83±0.25).

Table 3-3 Oxidant –Antioxidant Parameter for Patient Groups and Control Groups

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
TOS (µmol/L)	30	Po	1.23±0.52	1.03	1.42	Po	Pnon	0.00001
							Co	0.382
							Cnon	0.004
	30	Pnon	0.81±0.34	0.69	0.94	Pnon	Co	0.028
							Cnon	0.898
	15	Co	1.11±0.45	0.86	1.36	Co	Cnon	0.071
	15	Cnon	0.83±0.25	0.69	0.97			
MDA(µmol/L)	30	Po	2.95±1.52	2.38	3.52	Po	Pnon	0.00001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	1.33±0.55	1.12	1.54	Pnon	Co	0.736
							Cnon	0.819
	15	Co	1.22±0.48	0.95	1.49	Co	Cnon	0.925
	15	Cnon	1.26±0.73	0.85	1.66			
TAC (m mol/L)	30	Po	0.56±0.21	0.48	0.64	Po	Pnon	0.001
							Co	0.371
							Cnon	0.00001
	30	Pnon	0.82±0.22	0.74	0.91	Pnon	Co	0.046
							Cnon	0.004
	15	Co	0.64±0.14	0.56	0.72	Co	Cnon	0.00001
	15	Cnon	1.08±0.50	0.80	1.36			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese

Regarding the values of the parameters that characterize the oxidant/antioxidant balance, they were higher in diabetic patients compared to

healthy subjects, being statistically significant, resulting in a $p < 0.05$ for the total oxidant status (TOS). It has also been observed a decrease in the levels of superoxide dismutase (SOD) and slightly low values (statistically significant) for the total antioxidant status (TAS) in diabetics compared with healthy subjects, probably indicating a tendency of depletion of the body's antioxidants in an attempt to counterbalance the intensive oxidative stress (Mastronikolis, S., *et al.* 2022)

Free radicals and oxidative stress play a significant role in pathogenesis and progression of diabetic vascular complications. Oxidative stress is a condition induced in the body when the amount of reactive oxygen species (ROS) in cells surpasses the capacity of antioxidant, the natural defense of human body against adverse effects of ROS is through different enzymatic and non-enzymatic antioxidants, which regulate the production of free radicals and their metabolites (Bjørklund, *et al*. 2022 ;Wronka, *et al.* 2022).

Obesity and fat buildup may lead to reduced serum TAC levels, which, in turn, can indicate whole free radical activity. Although the free radical concetration was more pronounced in the obese diabetes patients, serum TAC levels in this group reduced. Reduced oxidative stress and lower TAC levels, together with increased belly fat, may be associated with cardiovascular events. (Khateeb, *et al*. 2022).

Overweight and specifically abdominal obesity increase oxidative stress, which is linked to several obesity-related disorders, such as atherosclerosis, diabetes, and arterial hypertension, according to the research showed by Uçkan, *et al* (Uçkan, *et al.* 2022). In healthy women, oxidative stress and TAC levels are independently related with the accumulation of visceral fat.

The main result of this study was that the TAC in obese patient was lower than controls. Wronka *et al* have also demonstrated that TAC was reduced in

obese patient especially with metabolic syndrome and they have commented that obese children with metabolic syndrome are prone to oxidative stress (Wronka, *et al*. 2022)

3.2.3. Determine the Serum Lipid Profile in Patients and Control Subjects

The results in Table 3-4 of TC, T.G, LDL-C, vLDL-C significantly ($P<0.01$) greater levels in diabetic obese patients group, when compared with the control obese group, control non obese and significant ($P<0.01$) elevation levels of diabetic non obese group when compared with healthy non obese and control obese .

Significant variations in level of HDL-C in obese diabetic patients group when compared with those of obese controls group. The values of serum HDL-C of obese diabetic patients group and of nonobese diabetic patients group were decrease when comparing with healthy group. Nosignificant variation is seen in all these four groups.

Table 3-4: Lipid profile parameters in patients and control groups.

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
T.G (mg/dL)	30	Po	292.30 ± 123.88	246.04	338.56	Po	Pnon	0.00001
							Co	0.382
							Cnon	0.004
	30	Pnon	214.75 ± 46.37	197.43	232.07	Pnon	Co	0.028
							Cnon	0.0.001
	15	Co	129.81 ± 15.20	121.39	138.23	Co	Cnon	0.422
	15	Cnon	106.90 ± 25.44	92.81	120.99			
T.C(mg/dL)	30	Po	301.32±68.04	275.91	336.72	Po	Pnon	0.00001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	232.11±27.33	221.91	242.32	Pnon	Co	0.00001
							Cnon	0.00001
	15	Co	135.00±26.97	120.06	149.93	Co	Cnon	0.558
	15	Cnon	125.14±33.09	106.82	143.47			

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
						Lower	Upper	
HDL-C (mg/dL)	30	Po	41.58± 6.91	39.00	44.16	P	Pnon	0.006
							Co	0.014
							Cnon	0.00001
	30	Pnon	46.88 ± 6.42	44.48	49.28	Pnon	Co	0.858

							Cnon	0.001
	15	-Co	47.39± 6.41	43.84	50.94	Co	Cnon	0.009
	15	Cnon	54.57 ± 10.25	48.89	60.25			
LDL-C (mg/dL)	30	Po	201.27±62.62	177.89	224.65	Po	Pnon	0.00001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	142.28±25.43	132.78	151.77	Pnon	Co	0.00001
							Cnon	
	15	Co	61.64±30.46	44.77	78.51	Co	Cnon	0.435
	15	Cnon	49.19±34.92	29.85	68.53			
VLDL-C (mg/dL)	30	Po	58.46±24.77	49.20	67.71	Po	Pnon	0.001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	42.95±9.27	39.48	46.41	Pnon	Co	0.001
							Cnon	0.00001
	15	Co	25.96±3.04	24.27	27.64	Co	Cnon	0.422
	15	Cnon	21.38±5.08	18.56	24.19			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese.TC: Total cholesterol, HDL-C: High density lipoprotein-Cholesterol, LDL-C: Low density lipoprotein-Cholesterol, VLDL-C: Very low density lipoprotein-Cholesterol, TG: Triglycerides.

The results of T.G, T.C, LDL-C in Table 3-4 demonstrate meaningfully ($P<0.05$) higher levels for fat diabetic patients group associated to nonobese diabetic patients. Significant variations in level of HDL-C in obese diabetic patients group when compared with obese controls group. There were a decrease of serum HDL-C levels for obese diabetic patients group compared with nonobese diabetic patients group.

When compared healthy obese group and healthy nonobese group with diabetic obesity and diabetic nonobese patients had significantly higher of T.C, LDL-C, VLDL-C and T.Gs levels, while HDL-C levels show a nonsignificant variation in these four groups (Ivanova, *et al.* 2017; Aluganti Narasimhulu, C., and Parthasarathy, 2022).

When LDL-C was studied in type 2 diabetic patients, it was found that the proportion of LDL-C was increased in plasma from these patients compared to control subjects and was not modified after glycemic optimization. LDL-C and 2-3 folds of increased ability to release MCP-1 and interleukin-8 (IL-8) in endothelial cells (Fruchart, *et al.* 2008; Gupta, and Gupta, 2016 ;Ghafouri, *et al.* 2022).

Wang, X.,*et al* found increase in blood cholesterol and LDL cholesterol, where the serum HDL cholesterol levels did not differ significantly between the two groups in their study (Wang, *et al.* 2022). The conclusion of our study T2DM is caused by an excessive amount of body fat storage, and the risk of T2DM grows linearly with an increase in BMI. As a result, the worldwide rise in the incidence of obesity has coincided with a rise in the prevalence of T2DM.

3.2.4. Determination Adiponectin in Diabetic Patients Groups and Control Groups

Serum levels of pro-inflammatory marker (Adiponectin) are measured in diabetic obese patients group, diabetic nonobese group, and control group**.** Adipo level comparison between different groups in Table 3-5. Adipo was significantly decreased in the patients obese compared to patients nonobese, (p=0.002). Similarly, in the patients obese compared controls non obese (p<0.001). while Adipo levels were no significant elevated in the Pnon compared to control nonobes, (p=0.00001). and for Pnon compared with Co (p=0.719).

Table 3-5 - The Comparison of Patient and Control Groups for *ADIPO (mg/L)*

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
ADIPO (mg/L)	30	Po	13.37±3.91	11.90	14.83	Po	Pnon	0.002
							Co	0.004
							Cnon	0.00001
	30	Pnon	16.55±3.21	15.35	17.76	Pnon	Co	0.719
							Cnon	0.00001
	15	Co	17.00±3.87	14.86	19.15	Co	Cnon	0.00001
	15	Cnon	23.20±5.10	20.38	26.03			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese The mean difference is significant at P≤ 0.05

Kawano and Arora,2009 found negative correlation between plasma adiponectin levels and body mass index (BMI) in men and women. Plasma adiponectin concentration was negatively correlated with percentage body fat and waist-depration ratio, while also having an inverse relationship with fasting plasma insulin concentration. The study helped to confirm a link between obesity and type 2 diabetes in association with low plasma adiponectin concentration.

The result of Cnop *et al* also show that plasma adiponectin concentration is more closely related to insulin sensitivity and fasting insulinemia than to glycemia and adiposity. The results suggested that type 2 diabetes and obesity in patients with low adiponectin levels was in large part attributable to insulin resistance and/or hyperinsulinemia (Cnop, M., *et al.* 2003; Momo, A., *et al.* 2022).

D'Oria, R., *et al* has been found that the adiposity associated with low circulating levels of adiponectin contains the expansion of visceral and abdominal adipose tissue rather than total body adiposity. The importance of this is related to the fact abdominal fat expansion has a greater effect on insulin resistance than total obesity (D'Oria, R., *et al.* 2022) .

Pathophysiological conditions, such as diabetes and obesity, have only decreased adiponectin; Therefore, strategies to increase adiponectin only lead to a logical approach that may provide a new treatment modality for obesity-related diseases, such as insulin resistance, T2DM and atherosclerosis. It is hoped that this data will be useful in developing treatments to counteract the devastating, painful and costly effects of obesity (Gonzalez, L. *et al.* 2018; Christen, T.,*et al.* 2022).

Cardiovascular disease (CVDs) was effect with obesity in different ways (Choi, *et al.* 2013; Zhang, *et al.* 2022). Many adipokines mediate the cross talk between vasculature, heart and adipose tissues in the "adipo-cardiovascular axis"; the altered release of adipokines promotes a prothrombotic state contributing to atherosclerosis disease (. Rega-Kaun, G. *et al.* 2013). Some studies indicate that adiponectin has a beneficial role in CVDs and atherosclerosis. Low serum adiponectin levels are predictors myocardial infarction and atherosclerosis (Lei, *et al.* 2022).

The anti-hormone antagonism of adiponectin, its association with insulin resistance and obesity, and the use of adiponectin and its receptors as a therapeutic measure (Kawano, and Arora, 2009; Al-Ameri, and AM AL-Mashhedy, L., 2021). Decrease in adiponectin is thought to play a central role in type 2 diabetes and is strongly associated with the likelihood of developing obesity-induced diabetes and cardiovascular disease (Battineni, *et al*. 2022)

3.2.4. Determination of Adiponectin Receptor 1 in Diabetic patients Groups and Control Groups

ADIPOR1 is significantly reduced in patients obese associated to obese healthy , ($p \leq 0.05$). anon-obese patients ($p \leq 0.05$) respectively. While AdiporR1 level comparison between different groups in Table 3-5. AdipoR1 was significantly decreased in the patients obese compared to patients nonobese, (p=0.00001). Similarly, in the patients obese compared controls non obese (p=0.00001). while AdipoR1 levels were no significant elevated in the Pnon compared to control obese, (p=0.185). and for Co compared with Cnon (p=0. 002).

Table 3-5 The Comparison of Patient and Control Groups for *ADIPOR1* (ng/mL)

Parameter	N	Group	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
ADIPOR1 ng/ml	30	Po	14.01±5.32	12.02	15.99	Po	Pnon	0.00001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	18.58 ±1.40	18.06	19.11	Pnon	Co	0.185
							Cnon	0.00001
	15	Co	20.16±2.44	18.80	21.51	Co	Cnon	0.002
	15	Cnon	24.59±4.04	22.35	26.83			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese

Several interactions and roles with some other biomolecules Monocyte Chemoattractant Protein -1 (MCP-1) has been clearly identified to form a sinister adipokine network causes of obesity-related insulin resistance and metabolic syndrome; PPARγ(Peroxisome proliferator-activated receptor γ) regulates HMW adiponectin (high molecular weight adiponectin), adiponectin and PPARα (Peroxisome proliferator-activated receptor α) regulates AdipoRs; dietary osmotin may act as a natural adiponectin receptor agonist.(Natalucci, *et al* ,2021)

Adiponectin also has a central action in regulating energy homeostasis by enhancing AMP-activated protein kinase activity in the arcuate hypothalamus (ARH) via its receptor AdipoR1 by stimulating food intake. Adiponectin also decreases energy expenditure. Fasting results in an increase in serum and cerebrospinal fluid levels of adiponectin and expression of AdipoR1 in the ARH, with this countered by refeeding. Therefore adiponectin stimulates food intake and decreases energy expenditure during fasting through its effects in the central nervous system (Kubota, *et al*. 2000; Battineni, *et al.* 2022).

3.2.5. Determination of Monocyte chemoattractant protein 1 in Diabetic patients Groups and Control Groups

MCP-1 is significantly reduced in patients obese compared with obese healthy , ($p > 0.05$). anon-obese patients ($p>0.05$) respectively . Monocyte chemoattractant protein 1 (MCP-1) level comparison between different groups in Table 3-7. MCP-1. was significantly increased in the patients obese compared to patients nonobese, ($p=0.00001$). Similarly, in the patients obese compared controls non obese ($p<0.001$). while MCP-1 levels were no significant elevated in the Pnon compared to control nonobes, ($p=0.253$). and for Pnon compared with Co ($p=0.846$).

Table 3-7 The Comparison of Patient and Control Groups for *MCP-1 pg\ml*

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
MCP-1 pg\ml.	30	Po	329.01±117.52	285.13	372.90	Po	Pnon	0.00001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	100.19±8.97	96.84	103.54	Pnon	Co	0.846
							Cnon	0.253
	15	Co	95.97±12.57	89.01	102.93	Co	Cnon	0.410
	15	Cnon	75.20±9.12	70.15	80.25			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese

Blood monocytes play a role in cytokine production, migration into infl amed adipose tissue, and vascular adhesion all of which contribute to the development of obesity comorbidities. Cytokines and chemokines, containing monocyte chemoattractant protein-1 (MCP-1) (Lumeng,., and Saltiel,., 2011; Enas *et al.* 2015).

The high levels of MCP-1 in obese patients were further increased by fructose consumption Furthermore, MCP-1 signaling has a direct role in the developmentof obesity. MCP-1 had angiogenic effect on endothelial cells and therefore it can contribute to the expansion and remodeling of adipose tissues. must be inhibit MCP-1 over-production and ameliorate obesity-related syndromes, such as insulin resistance and type 2 diabetes (Xiao, *et al* ,2022).

Despite increasing evidence that points to antiinflammatory action for adiponectin, a few in vitro studies, conducted in endothelial (Rovin, and Song, ,2006.) and monocytic cell lines produced contradictory results, and suggested that adiponectin actually has pro-inflammatory actions depending on the type

of adiponectin used and the conditions of stimulation (Tsatsanis, *.et al* ,2005; Domínguez, and Alonso-Castro, ,2022)

Piemonti, L.*et al* was found T2DM accounts for 95% of diabetic cases, and its cause is linked to obesity and insulin resistance. MCP-1 levels in the blood have been observed to be considerably higher in type 2 diabetes patients (Piemonti, *et al.* 2009; Sharma, *et al.* 2021).

The progression of diabetic atherosclerosis entails complex interactions between the modified low-density lipoproteins LDL isolated from type 2 diabetic subjects induced the mRNA expression of MCP-1 in cultured human endothelial cells (Castillo-Nunez, *et al.* 2022).

3.2.5. Determination of Plasminogen activation inhibitor-1 in Diabetic patients Groups and Control Groups

PAI-1 is significantly reduced in patients obese associated to obese healthy , ($p > 0.05$). anon-obese patients ($p>0.05$) respectively . Plasminogen activation inhibitor-1 (PAI-1) level comparison between different groups in Table 3-8. *PAI-1* was significantly increased in the patients obese compared to patients nonobese, ($p=0.00001$). While *PAI-1* levels were significant elevated in the Pnon compared to control obese, ($p=0.379$).

Table 3-8 The Comparison of Patient and Control Groups for *PAI-1* (ng/mL)

Parameter	N	Groups	Mean± SD	CI 95%		Compared groups		P value
				Lower	Upper			
SREPENE-1 (PAI-1) ng\ ml	30	Po	6.25±2.34	5.37	7.13	Po	Pnon	0.00001
							Co	0.00001
							Cnon	0.00001
	30	Pnon	4.03±2.23	3.20	4.86	Pnon	Co	0. 379
							Cno	0.00001
	15	Co	3.49±0.94	2.97	4.01	Co	Cnon	0.00001
	15	Cnon	0.72±0.16	0.63	0.81			

Po: patients obese , Pnon :patients non obese, Co :controls obese, Cnon: controls non obese

Plasminogen activation inhibitor-1 (PAI-1) was positively and adiponectin was negatively associated with body mass index, waist hip ratio (WHR), body fat mass, percent body fat, and all the parameters of MS, except HDL-C where the pattern reversed. WHR and triglycerides were independent predictors of adipokines in multiple regression analysis , Subjects with MS have lower adiponectin and higher PAI-1 levels compared to healthy controls. Lifestyle measures have been shown to improve the various components of MS, and hence there is an urgent need for public health measures to prevent the ongoing epidemic of diabetes and CVD (Alessi, and Juhan-Vague, 2006; Garg, *et al.* 2012; Levine, *et al.* 2021).

Morrow, G., *et al*. Found a metabolic syndrome and diabetes, plasminogen activator inhibitor-1 In individuals with T2DM, circulating PAI-1 levels are elevated, which contributes significantly to prothrombotic and proatherosclerotic alterations. Furthermore, plasma PAI-1 levels are elevated across the insulin resistance continuum, from the metabolic syndrome to prediabetes (a state of reduced glucose tolerance) to diabetes. Because both

obese and non-obese animals had elevated plasma PAI-1 levels in these conditions, obesity appears to play a substantial role.(Dyslipidemia, 2014;Morrow, *et al*. 2022)**.**

3.2.6. Determination of FSH in Diabetic patients Groups and Control Groups

In this study, FSH was measured in adult and postmenopausal women, and patients were compared with healthy people, and the results were obtained FSH in Follicular phase and FSH level postmenopausal ,in obese patient, Follicular (3.96±1.58), postmenopausal (29.44±1.79), patient non obese , Follicular (4.85±1.42), postmenopausal (29.73±1.99), control obese , Follicular (5.18±1.91), postmenopausal (30.42±2.60),control non obese, Follicular (6.63±1.79), postmenopausal (32.56±2.85). FSH Follicular phase was no significantly in the patients obese compared to patients nonobese (p=0.14) control obese (p=0.09) control non obese (p=0.001). while *FSH* levels were significant elevated in the Pnon compared to control obese, (p=0.642) and with control non obese(p=0.017),Cnon compared with Co (p=0.083).

The p value FSH level postmenopausal compared between Po with Pnon, Cnon and Co (p=0.001) ,(p=0.083) and (p=0.718) while Pnon with Co and Cnon (p=0.481) and (p=0.006) .Co compared C non (p=0.06)

Several studies have investigated the correlation between FSH level and MetS, lipid metabolism, dyslipidemia, and diabetes mellitus (DM) in postmenopausal women, the precise role of FSH in these metabolic dysfunctions in postmenopausal women is still poorly understood. (Stefanska, *et al.* 2012; Song, *et al.* 2016; Wang, *et al.* 2016; Lee, *et al.* 2022) were conducted this study to clarify the relationship between FSH level and MetS in postmenopausal women. In order to do so, we have analyzed the associations

between FSH and metabolic risk factors such as obesity, abdominal obesity, markers of insulin resistance, and adipokines (Moccia, *et al.* 2022)

The FSH level increases gradually during perimenopause and menopause in direct response to a decreased signal by endogenous estrogen (Shaw,.*et al.* 2010). Aging attenuates the pituitary response to gonadotropin hormone; the FSH level is also attenuated with aging in postmenopausal women (Shaw,.*et al.*2009) ,However, studies have also been reported that age does not affect FSH levels, showing inconsistent conclusions (Lee, *et al.*2022), there was no correlation between both age and years since menopause and FSH level.

The study showed that adiponectin is one of the independent variables of FSH level. Adiponectin plays a role in reducing the risk of metabolic syndrome by increasing insulin sensitivity and anti-inflammatory effect in adipose tissue (Lihn, *et al.* 2005). Previous studies showed that adiponectin level is negatively associated with estradiol level (Stefanska, *et al.*2012; SKONIECZNA-ŻYDECKA, *et al.* 2021).

3.2.7. Concentration of LH in Diabetic patients Groups and Control Groups

In this study, LH was measured in phase and postmenopausal women, and patients were compared with healthy people, and the results were obtained LH in Follicular phase and LH level postmenopausal, in obese patient, Follicular (3.96±1.58), postmenopausal (15.23±2.63), patient non obese, Follicular (10.36±2.63), postmenopausal- (16.36±2.64), control obese, Follicular (10.28±3.57), postmenopausal (16.28±3.57),control non obese, Follicular (11.37±4.97), postmenopausal (17.37±4.98). LH Follicular phase was no significantly in the patients obese compared to patients nonobese (p=0.355 ,control obese (p=0.472) control non obese (p=0.147). while *LH* levels were no significant elevated in the Pnon compared to control obese,

(p=0.96) and with control non obese(p=0.490),Cnon compared with Co (p=0.51).

P value LH level postmenopausal compared between Po with Pnon, Cnon and Co (p=0.335) ,(p=0.472) and (p=0.147) while Pnon with Co and Cnon (p=0.95) and (p=0.490) .Co compared C non (p=0.52)**.**

Significant differences in LH, FSH, or estrange conjugate. Early follicular phase LH pulse frequency did not differ from normal-weight women, but both amplitude and mean LH were dramatically reduced in obese women (0.8 ± 0.1 and 2.0 ± 0.3 IU/liter) compared with controls (1.6 ± 0.2 and 3.4 ± 0.2 IU/liter; $P < 0.01$) ,significant differences in LH, FSH, or estrone conjugate. Early follicular phase LH pulse frequency did not differ from normal-weight women (Jain, *et al.*2007; Koudele, *et al.*2022).

Jain, A. *et al.*2007 is demonstrating herein that obesity is associated with reduced central LH drive, as well as a large deficit in luteal Pdg (Pregnanediol glucuronide **)** excretion, High-BMI women were observed to secrete significantly smaller amplitude LH pulses but a similar pulse frequency to normal-weight women our findings indicate that deficient LH secretion, via impaired LH pulse amplitude, leads to inadequate luteal stimulation and reduced luteal Pdg in high-BMI women.

The gonadotropin dysfunction seen in PCOS may also be the result of hypothalamic and pituitary mechanisms as seen by increased LH pulse frequency and often elevated LH or LH/FSH ratio (WALDSTREICHER, J., *et al.*1988 Gambineri, *et al.* 2022). A relationship with adiposity similar to what we described has also been seen in PCOS. With increasing body weight, LH pulse amplitude is reduced in women with PCOS, although pulse frequency is increased compared with normally cycling women in both lean and obese PCOS (Taylor, *et al.*1997; Maya, and Misra,. 2022).

In Figure 1-3, the relationship between all the factors studied in the dissertation was clarified, and the relationship between its increase and decrease with diabetes and obesity was illustrated by arrows.

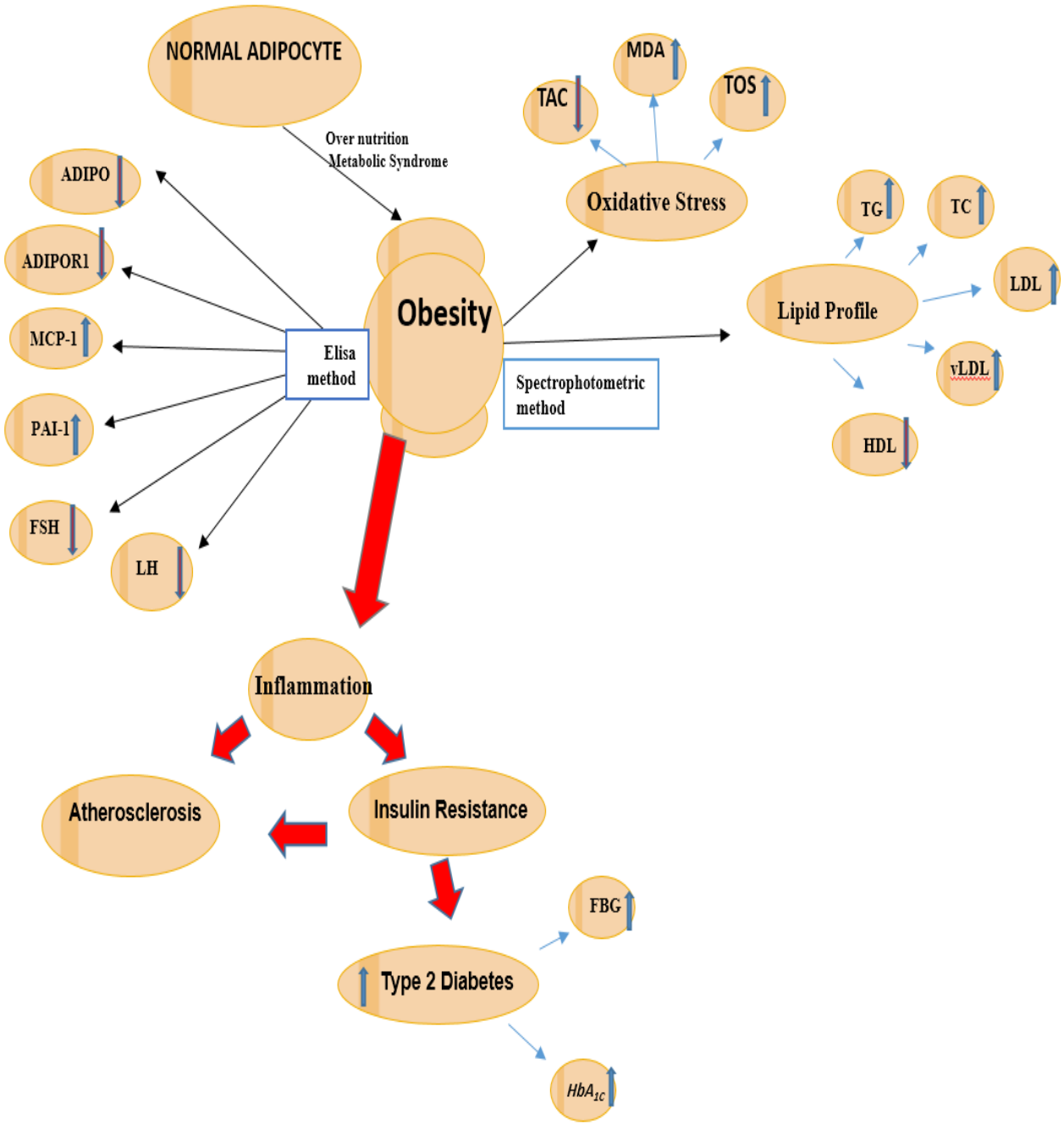


Figure 1-3 The Relationship between Parameter

3.3. Correlation Analysis

3.3.1. The Relevance of Adiponectin with the Biochemical Parameters in the diabetic Obese Patients

Table 3-9 shows significant positive correlations of diabetic obese patients obtained from HDL-C , LH, FSH, ADIPO, TAC, and ADIPOR1.

Significant negative correlations were obtained from Age, FBS, BMI, T.G, MDA ,LDL-C, MCP-1,PAI-1 , TOS and VLDL-C.

Table 3-9 The correlation of Adiponectin with concentrations of biochemical parameters in the diabetic obese patients.

Parameters	ADIPO (ng/mL)	
	r	P value
Age (years)	-0.122	0.519
BMI(kg/m^2)	-0.441	0.015
FBG(mg/dL)	-0.898	0.00001
T.C(mg/dL)	-0.686	0.00001
T.G(mg/dl)	-0.700	0.00001
HDL-C(mg/dL)	0.473	0.00001
Age (years)	-0.754	0.00001
BMI(kg/m^2)	-0.655	0.00001
MDA µmol /L	-0.509	0.004
TAC mmol/L	0.817	0.00001
TOS µmol /L	-0.179	0.341
ADIPOR1 ng/ml	0.811	0.00001
HbA_{1C}%	-0.394	0.031
PAI-1 mg/l	-0.830	0.0001
MCP-1mg/l	-0.641	0.0001
FSH IU/I	0.471	0.009
LH IU/I	0.240	0.201

Strong negative correlation between the levels of serum adiponectin and Fasting Blood Glucose, adiponectin and resistine. (P.value = 0.013, r = -7.9). (P.value = 0.019, r = -6.6). While showing in the other side strong positive

Correlation between the levels of serum resistine and Fasting Blood Glucose. (P.value = 0.015, r = 6.0) (Hussein, *et al.* 2022).

Adiponectin showed negative correlation with the body weight (r=-0.423, p=0.025) in the group of DM1 patients with nor mal BMI (Fanchin *et al.* 2005; Chen, *et al.* 2022) and find statistically significant relationship between adiponectin and HbA1c levels, which remains con sis tent with the results of other authors (Visser, J, *et al.* 2006; MALECHA-JĘDRASZEK, A, *et al.* 2012). However, Hehenkamp. w.. *et al.* have demonstrated the impact of glycemic control on adiponectin levels as confirmed by positive correlation of adiponectin with glycosylated he myoglobin levels (Hehenkamp, W, *et al.* 2006; Stanimirovic, J.*et al.* 2022).

3.3.2. The Relevance of MCP-1 with the Biochemical Parameters in the diabetic Obese Patients

Table (3-10) shows significant negative correlations of diabetic obese patients obtained from HDL-C , LH, FSH, TAC, ADIPO, and ADIPOR1.

significant positive correlations were obtained from Age, FBS, BMI, T.G, MDA , LDL-C, PAI-1 , TOS and vLDL-C.

Table 3-10 The correlation MCP-1 with concentrations of biochemical parameters in the diabetic obese patients.

Parameters	MCP-1(ng/mL)	
	r	P value
Age	0.251	0.181
Age (years)	0.428	0.018
BMI(kg/m^2)	0.715	0.00001
FBG(mg/dL)	0.336	0.069
T.C(mg/dL)	0.333	0.006
T.G(mg/dl)	-0.333	0.072
HDL-C(mg/dL)	0.703	0.00001
LDL-C (mg/dL)	0.436	0.016
VLDL-C (mg/dL)	0.308	0.09
HbA_{1C}%	0.398	0.029
MDA µmol /L	-0.619	0.00001
TAC mmol/L	0.199	0.291
ADIPOR1ng/ml	-0.676	0.00001
FSH IU/I	-0.364	0.048
LH IU/I	-0.263	0.159
PAI-1 mg/L	0.415	0.0001

3.3.3. The Relevance of PAI-1 with the Biochemical Parameters in the diabetic Obese Patients

Table 3-11 shows significant negative correlations of diabetic obese patients obtained from HDL-C, LH, FSH, TAC, ADIPO and ADIPOR1

significant positive correlations were obtained from Age, FBS, BMI, T.G, MDA , vLDL-c, TOS and vLDL-C

Table 3-11 The correlation PAI-1with concentrations of biochemical parameters in the diabetic obese patients.

Parameters	PAI1-1(ng/mL)	
	r	P value
Age	0.304	0.102
Age (years)	0.286	0.141
BMI(kg/m^2)	0.755	0.00001
FBG(mg/dL)	0.593	0.001
T.C(mg/dL)	0.611	0.00001
T.G(mg/dl)	-0.342	0.064
HDL-C(mg/dL)	0.697	0.00001
LDL-C (mg/dL)	0.577	0.001
VLDL-C (mg/dL)	0.534	0.002
HbA_{1C}%	0.195	0.300
MDA µmol /L	-0.563	0.001
TAC mmol/L	0.238	0.204
ADIPOR1ng/ml	-0.735	0.00001
FSH IU/I	-0.452	0.012
LH IU/I	-0.084	0.658

3.3.2. The Relevance of ADIPOR1 with Concentrations of Biochemical Parameters in the diabetic Obese Patients

Table 3-12 shows significant positive correlations of diabetic obese patients obtained from ADIPO, HDL-C , LH, FSH and TAC .

significant negative correlations were obtained from Age, FBS, BMI, T.G, MDA ,LDL-C, MCP-1,PAI-1 , TOS and vLDL –C.

Table 3-12 The correlation of ADIPOR1 with concentrations of biochemical parameters in the diabetic obese patients.

Parameters	ADIPOR1 (ng/mL)	
	r	P value
Age (years)	-0.065	0.730
BMI(kg/m^2)	-0.608	0.00001
FBG(mg/dL)	-0.831	0.00001
T.C(mg/dL)	-0.540	0.004
T.G(mg/dl)	-0.637	0.00001
HDL-C(mg/dL)	0.615	0.00001
LDL-C (mg/dL)	-0.792	0.00001
VLDL-C (mg/dL)	-0.554	0.001
HbA_{1C}%	-0.425	0. 019
MDA µmol /L	-0.636	0.00001
TAC mmol/L	0.660	0.00001
TOS µmol /L	-0.091	0.630
FSH IU/I	0.451	0.012
LH IU/I	0.322	0.082

3.4.Conclusions

1. The present study shows that the concentrations of anti-inflammatory Hormones (ADIPO and ADIPOR1) are reduced in diabetic obese patients and diabetic nonobese while compared healthy subjects .Therefore the development of diabetes obese patients can be predicted by the biomarker Adiponectin .

2. The findings reveal that pro-inflammatory Proteins (MCP-1 and PAI-1) are increased in patients (obesity and diabetic) It may be considered as a risk factor for metabolic syndrome like atherosclerosis and cardiovascular disease

3. The findings reveal that hormon (FSH and LH) is involved in change of T2DM as a result of obesity.

4. Anti- and pro-inflammatory cytokines were effected by obesity and diabetic.

3.5. Recommendations

1- Sequential **Plasminogen activator inhibitor-1,** Monocyte chemoattractant protein-1, Adiponectin and Adiponectin Receptor measurements should be made during and after a period of insulin sensitizing drug administration.

2- Adipocytokines measurements should be studied for long periods in obese individuals and individuals with cardiovascular disease.

3- Further studies on oxidative stress , related with insulin resistance

Reference

Abdul-Ghani, M. A., Tripathy, D., & DeFronzo, R. A. (2006). Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes care, 29(5), 1130-1139.

Abou-Samra, M., Selvais, C. M., Dubuisson, N., & Brichard, S. M. (2020). Adiponectin and its mimics on skeletal muscle: insulin sensitizers, fat burners, exercise mimickers, muscling pills… or everything together?. International journal of molecular sciences, 21(7), 2620

Adnan, M. T., Amin, M. N., Uddin, M. G., Hussain, M. S., Sarwar, M. S., Hossain, M. K., ... & Islam, M. S. (2019). Increased concentration of serum MDA, decreased antioxidants and altered trace elements and macro-minerals are linked to obesity among Bangladeshi population. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(2), 933-938.

Adorni, M. P., Ronda, N., Bernini, F., & Zimetti, F. (2021). High density lipoprotein cholesterol efflux capacity and atherosclerosis in cardiovascular disease: pathophysiological aspects and pharmacological perspectives. *Cells*, *10*(3), 574.

Aguayo-Mazzucato, C. (2020). Functional changes in beta cells during ageing and senescence. *Diabetologia*, *63*(10), 2022-2029.

Ahuja, R. P., Fletcher, J. M., Granger, L. A., Liu, C. C., Miessler, B., & Mitchell, M. A. (2022). Changes in glucose tolerance and insulin secretion in a cohort of cats with chronic obesity. *Canadian Journal of Veterinary Research*, *86*(3), 181-187.

Al Yafi, M., Nasif, A., Glosser, L. D., Ren, G., Ahemd, A., Nazzal, M., & Osman, M. (2022). The relationship between lower extremity amputation and body mass index. Vascular, 17085381221087824.

Al-Ameri, A. A., & AM AL-Mashhedy, L. (2021). The Association between Lipocalin 2 and obesity for diabetic Female Type II. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO, 8805-8814.

Al-Azemi, M., Omu, F. E., & Omu, A. E. (2004). The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Archives of gynecology and obstetrics, 270(4), 205-210.

Alberti, K. G. M. M., Zimmet, P., & Shaw, J. (2007). International Diabetes Federation: a consensus on Type 2 diabetes prevention. Diabetic Medicine, 24(5), 451-463.

Ali, N. (2011). Diabetes and you: A comprehensive, holistic approach. Rowman & Littlefield Publishers.

Alipio, Z., Liao, W., Roemer, E. J., Waner, M., Fink, L. M., Ward, D. C., & Ma, Y. (2010). Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic β-like cells. Proceedings of the National Academy of Sciences, 107(30), 13426-13431.

Alizadeh, H. (2022). Meteorin-like protein (Metrnl): A metabolic syndrome biomarker and an exercise mediator. Cytokine, 157, 155952.

Almubarak, F. (2016). The Association Between Known Risk Factors for Type 2 Diabetes, and the Body Mass Index of Diabetic Adults. University of Arkansas.

Aluganti Narasimhulu, C., & Parthasarathy, S. (2022). Preparation of LDL, Oxidation, Methods of Detection, and Applications in Atherosclerosis Research. In Atherosclerosis (pp. 213-246). Humana, New York, NY.

American Diabetes Association. (2014). Diagnosis and classification of diabetes mellitus. Diabetes care, 37(Supplement_1), S81-S90.

Amin, M. N., Liza, K. F., Sarwar, M., Ahmed, J., Adnan, M., Chowdhury, M. I., ... & Islam, M. S. (2015). Effect of lipid peroxidation, antioxidants, macro minerals and trace elements on eczema. Archives of dermatological research, 307(7), 617-623.

Amirkhizi, Farshad, Fereydoun Siassi, Mahmoud Djalali, and Abbas Rahimi Foroushani. 2010. “Evaluation of Oxidative Stress and Total Antioxidant Capacity in Women with General and Abdominal Adiposity.”

Obesity Research and Clinical Practice 4(3): e209–16. http://dx.doi.org/10.1016/j.orcp.2010.02.003.

Anandasundaram, B., Lane, D. A., Apostolakis, S., & Lip, G. Y. H. (2013). The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. Journal of Thrombosis and Haemostasis, 11(5), 975-987.

Andreadi, A., Bellia, A., Di Daniele, N., Meloni, M., Lauro, R., Della-Morte, D., & Lauro, D. (2022). The molecular link between oxidative stress, insulin resistance, and type 2 diabetes: A target for new therapies against cardiovascular diseases. Current Opinion in Pharmacology, 62, 85-96.

Anzueto, A., Frutos-Vivar, F., Esteban, A., Bensalami, N., Marks, D., Raymondos, K., ... & Ferguson, N. D. (2011). Influence of body mass index on outcome of the mechanically ventilated patients. Thorax, 66(1), 66-73.

Apak, Reşat et al. 2005. "Total Antioxidant Capacity Assay of Human Serum Using Copper(II)-Neocuproine as Chromogenic Oxidant: The CUPRAC Method." Free Radical Research 39(9): 949–61.

Arakelyan, A., Petrkova, J., Hermanova, Z., Boyajyan, A., Lukl, J., & Petrek, M. (2005). Serum levels of the MCP-1 chemokine in patients with ischemic stroke and myocardial infarction. Mediators of inflammation, 2005(3), 175-179.

Ardisson Korat, A. V., Willett, W. C., & Hu, F. B. (2014). Diet, lifestyle, and genetic risk factors for type 2 diabetes: a review from the Nurses' Health Study, Nurses' Health Study 2, and Health Professionals' Follow-up Study. Current nutrition reports, 3(4), 345-354.

Artham, S. M., Lavie, C. J., Milani, R. V., & Ventura, H. O. (2008). The obesity paradox: impact of obesity on the prevalence and prognosis of cardiovascular diseases. Postgraduate medicine, 120(2), 34-41.

Asif, M. (2014). The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. Journal of education and health promotion, 3.

Association, A. D. (2001). Hyperglycemic crises in patients with diabetes mellitus. Diabetes Care, 24(1), 154-161.

Astrup, A. (2001). Healthy lifestyles in Europe: prevention of obesity and type II diabetes by diet and physical activity. Public health nutrition, 4(2b), 499-515.

Bagdade, J. D., Bierman, E. L., & Porte, D. (1967). The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. The Journal of clinical investigation, 46(10), 1549-1557.

Bailey, C. J. (2017). Metformin: historical overview. Diabetologia, 60(9), 1566-1576.

Banerjee, A., Pathak, S., & Duttaroy, A. K. (2022). Dietary Fats and the Gut Microbiota: Their impacts on lipid-induced metabolic syndrome. Journal of Functional Foods, 91, 105026.

Barham, Denise, and P. Trinder. 1972. "An Improved Colour Reagent for the Determination of Blood Glucose by the Oxidase System." The Analyst 97(1151): 142–45.

Berman, C., Naguib, M., Hegedus, E., & Vidmar, A. P. (2022). Topiramate for Weight Management in Children with Severe Obesity. Childhood Obesity.

Bhatti, J. S., Sehrawat, A., Mishra, J., Sidhu, I. S., Navik, U., Khullar, N., ... & Reddy, P. H. (2022). Oxidative stress in the pathophysiology of type 2 diabetes and related complications: Current therapeutics strategies and future perspectives. Free Radical Biology and Medicine.

Bhatti, M. S., Akbri, M. Z. A., & Shakoor, M. (2001). Lipid profile in obesity. *Journal of Ayub Medical College Abbottabad*, *13*(1), 31-33.

Bilgili, S., Celebiler, A. C., Dogan, A., & Karaca, B. (2008). Inverse relationship between adiponectin and plasminogen activator inhibitor-1 in metabolic syndrome patients. Endocrine regulations, 42(2-3), 63-68.

Bishop, C. W., Strugnell, S. A., Csomor, P., Kaiser, E., & Ashfaq, A. (2022). Extended-Release Calcifediol Effectively Raises Serum Total 25-Hydroxyvitamin D Even in Overweight Nondialysis Chronic Kidney

Disease Patients with Secondary Hyperparathyroidism. American Journal of Nephrology, 1-9.

Blüher, M. (2019). Obesity: global epidemiology and pathogenesis. Nature Reviews Endocrinology, 15(5), 288-298.

Boland, B. B., Rhodes, C. J., & Grimsby, J. S. (2017). The dynamic plasticity of insulin production in β-cells. Molecular metabolism, 6(9), 958-973.

Boyle, J. P., Thompson, T. J., Gregg, E. W., Barker, L. E., & Williamson, D. F. (2010). Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Population health metrics, 8(1), 1-12.

Bozkurt, S., Coskun, H., Kadioglu, H., Memmi, N., Cipe, G., Ersoy, Y. E., ... & Muslumanoglu, M. (2013). Remission of ulcerated necrobiosis lipoidica diabeticorum after bariatric surgery. Case Reports in Dermatological Medicine, 2013.

Braoudaki, M., Ahmad, M. S., Mustafov, D., Seriah, S., Siddiqui, M. N., & Siddiqui, S. S. (2022, June). Chemokines and chemokine receptors in colorectal cancer; multifarious roles and clinical impact. In Seminars in Cancer Biology. Academic Press.

Brehm, A., Krssak, M., Schmid, A. I., Nowotny, P., Waldhäusl, W., & Roden, M. (2006). Increased lipid availability impairs insulin-stimulated ATP synthesis in human skeletal muscle. Diabetes, 55(1), 136-140.

Carchman, R. M., Dechert-Zeger, M., Calikoglu, A. S., & Harris, B. D. (2005). A new challenge in pediatric obesity: pediatric hyperglycemic hyperosmolar syndrome. Pediatric Critical Care Medicine, 6(1), 20-24.

Carmichael, L., Keske, M. A., Betik, A. C., Parker, L., Brayner, B., Roberts-Thomson, K. M., ... & Kaur, G. (2022). Is vascular insulin resistance an early step in diet-induced whole-body insulin resistance?. Nutrition & Diabetes, 12(1), 1-12.

Chandi, M. (2018). Inhibition of insulin secretion in β-cells exposed to arsenic, cadmium and manganese is associated with altered microRNA expression.

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., ... & Mirza, W. (2017). Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Frontiers in endocrinology, 8, 6.

Chen, L., Magliano, D. J., & Zimmet, P. Z. (2012). The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology, 8(4), 228-236.

Chen, X., Wang, K., Lu, T., Wang, J., Zhou, T., Tian, J., ... & Zhou, Q. (2022). Adiponectin is negatively associated with disease activity and Sharp score in treatment-naïve Han Chinese rheumatoid arthritis patients. Scientific reports, 12(1), 1-7.

Cherrington, A. D. (1999). Banting Lecture 1997. Control of glucose uptake and release by the liver in vivo. Diabetes, 48(5), 1198-1214.

Cho, N. H., Ku, E. J., Jung, K. Y., Oh, T. J., Kwak, S. H., Moon, J. H., ... & Choi, S. H. (2020). Estimated association between cytokines and the progression to diabetes: 10-year follow-up from a community-based cohort. The Journal of Clinical Endocrinology & Metabolism, 105(3), e381-e389.

Choi, J. W., Han, E., & Kim, T. H. (2022). Risk of Hypertension and Type 2 Diabetes in Relation to Changes in Alcohol Consumption: A Nationwide Cohort Study. International Journal of Environmental Research and Public Health, 19(9), 4941.

Choi, J. Y., Shin, J., & Baek, S. (2021). Gender-based comparison of factors affecting regular exercise of patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) based on the 7th Korea National Health and Nutrition Examination Survey (KNHANES). Plos one, 16(9), e0257822.

Choi, S. H., Hong, E. S., & Lim, S. (2013). Clinical implications of adipocytokines and newly emerging metabolic factors with relation to insulin resistance and cardiovascular health. Frontiers in endocrinology, 4, 97.

Chung, W. K. (2012). An overview of mongenic and syndromic obesities in humans. Pediatric blood & cancer, 58(1), 122-128.

Cioana, M., Deng, J., Hou, M., Nadarajah, A., Qiu, Y., Chen, S. S. J., ... & Samaan, M. C. (2021). Prevalence of hypertension and albuminuria in pediatric type 2 diabetes: a systematic review and meta-analysis. JAMA network open, 4(4), e216069-e216069.

Cnop, M., Havel, P. J., Utzschneider, K. M., Carr, D. B., Sinha, M. K., Boyko, E. J., ... & Kahn, S. E. (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia, 46(4), 459-469.

Cohen, K. E., Katunaric, B., Schulz, M. E., SenthilKumar, G., Young, M. S., Mace, J. E., & Freed, J. K. (2022). Role of Adiponectin Receptor 1 in Promoting Nitric Oxide-Mediated Flow-Induced Dilation in the Human Microvasculature. Frontiers in Pharmacology, 13, 875900.

Cottam, D. R., Mattar, S. G., Barinas-Mitchell, E., Eid, G., Kuller, L., Kelley, D. E., & Schauer, P. R. (2004). The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obesity surgery, 14(5), 589-600.

Cox, C. L., Stanhope, K. L., Schwarz, J. M., Graham, J. L., Hatcher, B., Griffen, S. C., ... & Havel, P. J. (2011). Circulating concentrations of monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and soluble leukocyte adhesion molecule-1 in overweight/obese men and women consuming fructose-or glucose-sweetened beverages for 10 weeks. The Journal of Clinical Endocrinology & Metabolism, 96(12), E2034-E2038.

Cui, H., Zhao, G., Liu, R., Zheng, M., Chen, J., & Wen, J. (2012). FSH stimulates lipid biosynthesis in chicken adipose tissue by upregulating the expression of its receptor FSHR. Journal of lipid research, 53(5), 909-917.

Cui, X., Feng, J., Wei, T., Gu, L., Wang, D., Lang, S., ... & Hong, T. (2022). Pro-α-cell-derived β-cells contribute to β-cell neogenesis induced by antagonistic glucagon receptor antibody in type 2 diabetic mice. Iscience, 25(7), 104567.

Cushing, S. D., Berliner, J. A., Valente, A. J., Territo, M. C., Navab, M., Parhami, F., ... & Fogelman, A. M. (1990). Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human

endothelial cells and smooth muscle cells. Proceedings of the National Academy of Sciences, 87(13), 5134-5138.

Cusi, K., & DeFronzo, R. A. (1998). Metformin: a review of its metabolic effects. Diabetes Reviews, 6(2), 89-131.

Dart, A. (2010). The natural history of youth onset type 2 diabetes mellitus. University of Manitoba (Canada).…

de Wit, A. E. (2021). From academia to society–improving the quality of science journalism. Can hormones get you down?, 223.

DeFronzo, R. A., Eldor, R., & Abdul-Ghani, M. (2013). Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes care, 36(Supplement_2), S127-S138.

Delaney, M. F., Zisman, A., & Kettyle, W. M. (2000). Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinology and metabolism clinics of North America, 29(4), 683-705.

Deshmane, S. L., Kremlev, S., Amini, S., & Sawaya, B. E. (2009). Monocyte chemoattractant protein-1 (MCP-1): an overview. Journal of interferon & cytokine research, 29(6), 313-326.

Després, J. P., & Lemieux, I. (2006). Abdominal obesity and metabolic syndrome. Nature, 444(7121), 881-887.

Devi, L. A. (2000). G-protein-coupled receptor dimers in the lime light. Trends in Pharmacological Sciences, 21(9), 324-326.

Domínguez, F., & Alonso-Castro, Á. (2022). Adipokines, Possible Biomarkers and Therapeutic Targets in Obesity and Related Pathologies. Diabesity: A Multidisciplinary Approach, 58.

Du, A. L., Tully, J. L., Curran, B. P., & Gabriel, R. A. (2022). Obesity and outcomes in patients undergoing upper airway surgery for obstructive sleep apnea. PloS one, 17(8), e0272331.

Duncombe, S. L., Barker, A. R., Bond, B., Earle, R., Varley-Campbell, J., Vlachopoulos, D., ... & Stylianou, M. (2022). School-based high-

intensity interval training programs in children and adolescents: A systematic review and meta-analysis. *PloS one*, *17*(5), e0266427.

Dyslipidemia, H. (2014). 10 Vascular Biology of Atherosclerosis in Patients with Diabetes. Diabetes in Cardiovascular Disease: A Companion to Braunwald's Heart Disease E-Book, 7, 111.

Elena, P., Päivi, H., Heini, H., & Saara, M. (2022). Glycaemic control in insulin deficient patients using different insulin delivery and glucose sensoring devices: cross-sectional real-life study. Diabetes Epidemiology and Management, 100072.

Enas R, A. H., Azza A, A. S., Rania N, S., Eman R, Y., Mones M, A. S., Amr Said, M., & Nadia A, M. (2015). Serum levels of monocyte chemoattractant protein-1, interlukin-6, and paraoxonase-1 in childhood obesity.

Erel, Ozcan. 2005. "A New Automated Colorimetric Method for Measuring Total Oxidant Status." Clinical Biochemistry 38(12): 1103–11.

Ervin, R. B. (2009). Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006.

Fanchin, R., Taieb, J., Lozano, D. H. M., Ducot, B., Frydman, R., & Bouyer, J. (2005). High reproducibility of serum anti-Müllerian hormone measurements suggests a multi-staged follicular secretion and strengthens its role in the assessment of ovarian follicular status. Human Reproduction, 20(4), 923-927.

Farooqi, I. S., & O Rahilly, S. (2004). Monogenic human obesity syndromes. Recent progress in hormone research, 59, 409-424.

Fernández-Millán, E., & Guillén, C. (2022). Multi-organ crosstalk with endocrine pancreas: A focus on how gut microbiota shapes pancreatic Beta-cells. Biomolecules, 12(1), 104.

Ferreira, V. L., Borba, H. H., Bonetti, A. D. F., Leonart, L., & Pontarolo, R. (2018). Cytokines and interferons: types and functions. *Autoantibodies and cytokines*, *13*.

Fonseca, V. A. (2009). Defining and characterizing the progression of type 2 diabetes. Diabetes care, 32(suppl 2), S151-S156.

Fowler, M. J. (2008). Microvascular and macrovascular complications of diabetes. Clinical diabetes, 26(2), 77-82.

Freitas Lima, L. C., Braga, V. D. A., do Socorro de França Silva, M., Cruz, J. D. C., Sousa Santos, S. H., de Oliveira Monteiro, M. M., & Balarini, C. D. M. (2015). Adipokines, diabetes and atherosclerosis: an inflammatory association. *Frontiers in physiology*, *6*, 304.

Fried, S. K., Bunkin, D. A., & Greenberg, A. S. (1998). Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. The Journal of Clinical Endocrinology & Metabolism, 83(3), 847-850.

Fruchart, J. C., Sacks, F., Hermans, M. P., Assmann, G., Brown, W. V., Ceska, R., ... & Residual Risk Reduction Initiative. (2008). The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. The American journal of cardiology, 102(10), 1K-34K.

Frühbeck, G., & Salvador, J. (2004). Role of adipocytokines in metabolism and disease. *Nutrition Research*, *24*(10), 803-826.

Fujioka, K. (2005). Follow-up of nutritional and metabolic problems after bariatric surgery. Diabetes care, 28(2), 481-484.

Gambineri, A., Pelusi, C., Vicennati, V., Pagotto, U., & Pasquali, R. (2002). Obesity and the polycystic ovary syndrome. International journal of obesity, 26(7), 883-896.

Garg, M. K., Dutta, M. K., & Mahalle, N. (2012). Adipokines (adiponectin and plasminogen activator inhhibitor-1) in metabolic syndrome. Indian journal of endocrinology and metabolism, 16(1), 116.

Gastaldelli, A., Gaggini, M., & DeFronzo, R. A. (2017). Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio Metabolism Study. Diabetes, 66(4), 815-822.

Gavin, K. M., & Bessesen, D. H. (2020). Sex differences in adipose tissue function. *Endocrinology and Metabolism Clinics*, *49*(2), 215-228.

Genuth, S. (1992). Management of the adult onset diabetic with sulfonylurea drug failure. Endocrinology and metabolism clinics of North America, 21(2), 351-370.

Gheitasi, I., Savari, F., Akbari, G., Mohammadi, J., Fallahzadeh, A. R., & Sadeghi, H. (2022). Molecular Mechanisms of Hawthorn Extracts in Multiple Organs Disorders in Underlying of Diabetes: A Review. International Journal of Endocrinology, 2022.

Golay, A., & Ybarra, J. (2005). Link between obesity and type 2 diabetes. Best practice & research Clinical endocrinology & metabolism, 19(4), 649-663.

Goldstein, D. P., & Kosasa, T. S. (1975). The subunit radioimmunoassay for hCG-Clinical application. Progress in Gynecology, 6, 145-184.

Gonzalez, L. L., Garrie, K., & Turner, M. D. (2018). Type 2 diabetes–an autoinflammatory disease driven by metabolic stress. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1864(11), 3805-3823.

Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B., & Dawber, T. R. (1977). High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. The American journal of medicine, 62(5), 707-714.

Gou, W., Ling, C. W., He, Y., Jiang, Z., Fu, Y., Xu, F., ... & Zheng, J. S. (2021). Interpretable machine learning framework reveals robust gut microbiome features associated with type 2 diabetes. Diabetes Care, 44(2), 358-366.

Grant, P. J. (2007). Diabetes mellitus as a prothrombotic condition. Journal of internal medicine, 262(2), 157-172.

Greenberg, A. S., & Obin, M. S. (2006). Obesity and the role of adipose tissue in inflammation and metabolism. The American journal of clinical nutrition, 83(2), 461S-465S.

Griffin, M. J. (2022). On the Immunometabolic Role of NF-κB in Adipocytes. Immunometabolism, 4(1).

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice, 103(2), 137-149.

Guillausseau, P. J., Meas, T., Virally, M., Laloi-Michelin, M., Médeau, V., & Kevorkian, J. P. (2008). Abnormalities in insulin secretion in type 2 diabetes mellitus. Diabetes & metabolism, 34, S43-S48.

Gungor, N., Thompson, T., Sutton-Tyrrell, K., Janosky, J., & Arslanian, S. (2005). Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. Diabetes care, 28(5), 1219-1221.

Guo, F., Moellering, D. R., & Garvey, W. T. (2014). Use of HbA1c for diagnoses of diabetes and prediabetes: comparison with diagnoses based on fasting and 2-hr glucose values and effects of gender, race, and age. Metabolic syndrome and related disorders, 12(5), 258-268.

Gupta, P., & Gupta, S. (2016). Evaluation of Lipid Profile in Type-II Diabetes Mellitus with Obesity. jouranl of midical scince and clinical Research ,88(5), 2455-0450.

Hallenborg, P., Jensen, B. A. H., Fjære, E., Petersen, R. K., Belmaâti, M. S., Rasmussen, S. S., ... & Blagoev, B. (2021). Adipose MDM2 regulates systemic insulin sensitivity. *Scientific reports*, *11*(1), 1-17.

Haslam, D. (2010). Obesity and diabetes: the links and common approaches. Primary care diabetes, 4(2), 105-112.

Hehenkamp, W. J., Looman, C. W., Themmen, A. P., de Jong, F. H., Te Velde, E. R., & Broekmans, F. J. (2006). Anti-Mullerian hormone levels in the spontaneous menstrual cycle do not show substantial fluctuation. The Journal of Clinical Endocrinology & Metabolism, 91(10), 4057-4063.

Henquin, J. C. (2004). Pathways in beta-cell stimulus-secretion coupling as targets for therapeutic insulin secretagogues. Diabetes, 53(suppl_3), S48-S58.

Hillock-Watling, C., & Gotlieb, A. I. (2022). The pathobiology of perivascular adipose tissue (PVAT), the fourth layer of the blood vessel wall. Cardiovascular Pathology, 107459.

Hadwan, M. H. (2008). The activities of Catalase in the Spermatozoa and Seminal Plasma of Patients with Asethenospermia; and their Relationship with Oxidants and Antioxidants. Iraqi Natl J Chem, 31, .514-521

Hayyan M, Hashim MA, AlNashef IM. Superoxide ion: generation and chemical implications. Chemical reviews. 2016;116(5):3029-3085

Hoogeveen, E. K. (2022). The Epidemiology of Diabetic Kidney Disease. Kidney and Dialysis, 2(3), 433-442.

Horton, E. S., Silberman, C., Davis, K. L., & Berria, R. (2010). Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. Diabetes care, 33(8), 1759-1765.

Howlader, M., Sultana, M. I., Akter, F., & Hossain, M. M. (2021). Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. Heliyon, 7(8), e07851.

Huang, X., Huang, X., Guo, H., Li, J., Zhou, C., Huang, Y., ... & Xie, C. (2022). Intermittent hypoxia-induced METTL3 downregulation facilitates MGLL-mediated lipolysis of adipocytes in OSAS. Cell death discovery, 8(1), 1-10.

Hussein, S. E. O., Osman, A. L., Higazi, H. M., Ali, S., & Alfeel, A. H. (2022). Influence of BMI on Serum Adiponectin, Resistine, and FBG among Overweight and Obese Females Diabetic Patient Type2. Open Access Macedonian Journal of Medical Sciences, 10(B), 1218-1221.

International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care, 2009, 32:1327-1334.

Ivanova, E. A., Myasoedova, V. A., Melnichenko, A. A., Grechko, A. V., & Orekhov, A. N. (2017). Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. Oxidative medicine and cellular longevity, 2017.

Jain, A., Polotsky, A. J., Rochester, D., Berga, S. L., Loucks, T., Zeitlian, G., ... & Santoro, N. (2007). Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. The Journal of Clinical Endocrinology & Metabolism, 92(7), 2468-2473.

Jeyabalan, A., Hubel, C. A., & Davidge, S. T. (2022). Cardiometabolic Antecedents of Preeclampsia. In *Chesley's Hypertensive Disorders in Pregnancy* (pp. 245-264). Academic Press.

Jung, U. J., & Choi, M. S. (2014). Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. International journal of molecular sciences, 15(4), 6184-6223.

Jwad, S. M., & AL-Fatlawi, H. Y. (2022). Types of Diabetes and their Effect on the Immune System. Journal of Advances in Pharmacy Practices (e-ISSN: 2582-4465), 21-30.

Kadowaki, T. (2000). Insights into insulin resistance and type 2 diabetes from knockout mouse models. The Journal of clinical investigation, 106(4), 459-465.

Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. The Lancet, 383(9922), 1068-1083.

Kannel, W. B., Wilson, P. W., & Zhang, T. J. (1991). The epidemiology of impaired glucose tolerance and hypertension. American heart journal, 121(4), 1268-1273.

Karamanakos, G., Kokkinos, A., Dalamaga, M., & Liatis, S. (2022). Highlighting the Role of Obesity and Insulin Resistance in Type 1 Diabetes and Its Associated Cardiometabolic Complications. Current Obesity Reports, 1-23.

Karim, R. M., Naser, M. D., & AL-Fartosi, A. J. (2011). Lipid peroxidation and alkaline phosphotase levels in gastropod Lymnaea Radix cor (Annandale and Prashad, 1919) exposed to sublethal concentrations of endosulfan. Al-Kufa University Journal for Biology, 3(2).

Kawano, J., & Arora, R. (2009). The role of adiponectin in obesity, diabetes, and cardiovascular disease. Journal of the cardiometabolic syndrome, 4(1), 44-49.

Kawano, J., & Arora, R. (2009). The role of adiponectin in obesity, diabetes, and cardiovascular disease. Journal of the cardiometabolic syndrome, 4(1), 44-49.

Kazemi-Bonchenari, M., Khanaki, H., Jafari, A., Eghbali, M., Poorhamdollah, M., & Ghaffari, M. H. (2022). Milk feeding level and starter protein content: Effects on growth performance, blood metabolites, and urinary purine derivatives of Holstein dairy calves. Journal of Dairy Science

Keeter, W. C., Ma, S., Stahr, N., Moriarty, A. K., & Galkina, E. V. (2022, March). Atherosclerosis and multi-organ-associated pathologies. In Seminars in Immunopathology (pp. 1-12). Springer Berlin Heidelberg.

Kershaw, E. E., & Flier, J. S. (2004). Adipose tissue as an endocrine organ. The Journal of Clinical Endocrinology & Metabolism, 89(6), 2548-2556.

Khosla, S., Melton III, L. J., Atkinson, E. J., O'fallon, W. M., Klee, G. G., & Riggs, B. L. (1998). Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. The Journal of Clinical Endocrinology & Metabolism, 83(7), 2266-2274.+5+64

Klein, S., Gastaldelli, A., Yki-Järvinen, H., & Scherer, P. E. (2022). Why does obesity cause diabetes?. *Cell metabolism*, *34*(1), 11-20.

Kopelman, P. G. (2000). Obesity as a medical problem. Nature, 404(6778), 635-643.

Kopelman, P. G. (2000). Obesity as a medical problem. Nature, 404(6778), 635-643.

Koudele, A., Levy, G., Eyvazzadeh, A., Park, J., Klein, J., & BECKLEY, A. (2022). The predic Hartz, A. J., Barboriak, P. N., Wong, A., Katayama, K. P., & Rimm, A. A. (1979). The association of obesity with infertility and related menstural abnormalities in

women. International journal of obesity, 3(1), 57-73.tive value of urinary Progesterone metabolite PdG testing in pregnancy outcomes.

Kubota, N., Yano, W., Kubota, T., Yamauchi, T., Itoh, S., Kumagai, H., ... & Kadowaki, T. (2007). Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell metabolism, 6(1), 55-68.

Kushner, Robert, Victor Lawrence, and Sudhesh Kumar. 2013. "The Genetic Basis of Obesity." Practical Manual of Clinical Obesity: 13–24.

Kyrou, I., Randeva, H. S., Tsigos, C., Kaltsas, G., & Weickert, M. O. (2018). Clinical problems caused by obesity. Endotext [Internet].

Lang, S., & Schnabl, B. (2020). Microbiota and fatty liver disease—the known, the unknown, and the future. *Cell host & microbe*, *28*(2), 233-244.

Lee, M. K., Cooney, O. D., Lin, X., Nadarajah, S., Dragoljevic, D., Huynh, K., ... & Loh, K. (2022). Defective AMPK regulation of cholesterol metabolism accelerates atherosclerosis by promoting HSPC mobilization and myelopoiesis. Molecular Metabolism, 61, 101514.

Lee, S. W., Hwang, I. S., Jung, G., Kang, H. J., & Chung, Y. H. (2022). Relationship between metabolic syndrome and follicle-stimulating hormone in postmenopausal women. Medicine, 101(18), e29216-e29216.

Lembo, E., Russo, M. F., Verrastro, O., Anello, D., Angelini, G., Iaconelli, A., ... & Capristo, E. (2022). Prevalence and predictors of non-alcoholic steatohepatitis in subjects with morbid obesity and with or without type 2 diabetes. Diabetes & Metabolism, 48(5), 101363.

Leonard, E. J., & Yoshimura, T. (1990). Human monocyte chemoattractant protein-1 (MCP-1). *Immunology today*, *11*, 97-101.

Leurs, P. B., Stolk, R. P., Hamulyak, K., Van Oerle, R., Grobbee, D. E., & Wolffenbuttel, B. H. (2002). Tissue factor pathway inhibitor and other endothelium-dependent hemostatic factors in elderly individuals with normal or impaired glucose tolerance and type 2 diabetes. Diabetes Care, 25(8), 1340-1345.

Levitsky, L. L., Drews, K. L., Haymond, M., Glubitosi-Klug, R. A., Katz, L. E. L., Mititelu, M., ... & TODAY Study Group. (2022). The obesity paradox: Retinopathy, obesity, and circulating risk markers in youth with type 2 diabetes in the TODAY Study. Journal of Diabetes and its Complications, 108259.

Li, C. W., Yu, K., Shyh-Chang, N., Jiang, Z., Liu, T., Ma, S., ... & Liu, G. S. (2022). Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. *Journal of Cachexia, Sarcopenia and Muscle*, *13*(2), 781-794.

Lihn, A. S., Bruun, J. M., He, G., Pedersen, S. B., Jensen, P. F., & Richelsen, B. (2004). Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. *Molecular and cellular endocrinology*, *219*(1-2), 9-15.

Lihn, A. S., Pedersen, S. B., & Richelsen, B. (2005). Adiponectin: action, regulation and association to insulin sensitivity. Obesity reviews, 6(1), 13-21.

Lim, P., & Bleich, D. (2022). Revisiting cardiovascular risk reduction in type 2 diabetes and dyslipidemia. International Journal of Cardiology Cardiovascular Risk and Prevention, 200141.

Lok, K. H., Wareham, N. J., Nair, R. S., How, C. W., & Chuah, L. H. (2022). Revisiting the concept of incretin and enteroendocrine L-cells as type 2 diabetes mellitus treatment. Pharmacological Research, 106237.

Lone, I. M., & Iraqi, F. A. (2022). Genetics of murine type 2 diabetes and comorbidities. Mammalian Genome, 1-16.

Lu, M., Tang, Q., Olefsky, J. M., Mellon, P. L., & Webster, N. J. (2008). Adiponectin activates adenosine monophosphate-activated protein kinase and decreases luteinizing hormone secretion in LβT2 gonadotropes. Molecular Endocrinology, 22(3), 760-771.

Lumeng, C. N., & Saltiel, A. R. (2011). Inflammatory links between obesity and metabolic disease. The Journal of clinical investigation, 121(6), 2111-2117.

Ma, L. J., Mao, S. L., Taylor, K. L., Kanjanabuch, T., Guan, Y., Zhang, Y., ... & Fogo, A. B. (2004). Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. Diabetes, 53(2), 336-346.

Maahs, D. M., West, N. A., Lawrence, J. M., & Mayer-Davis, E. J. (2010). Epidemiology of type 1 diabetes. Endocrinology and Metabolism Clinics, 39(3), 481-497.

MALECHA-JĘDRASZEK, A. R. L. E. T. A., BURSKA, A., DONICA, H., MATUSZEK, B., & NOWAKOWSKI, A. (2012). Serum adiponectin concentration in patients with type 1 diabetes.

Martín-Timón, I., Sevillano-Collantes, C., Segura-Galindo, A., & del Cañizo-Gómez, F. J. (2014). Type 2 diabetes and cardiovascular disease: have all risk factors the same strength?. World journal of diabetes, 5(4), 444.

Maya, J., & Misra, M. (2022). The female athlete triad: review of current literature. Current Opinion in Endocrinology & Diabetes and Obesity, 29(1), 44-51.

Mehran, A. E., Templeman, N. M., Brigidi, G. S., Lim, G. E., Chu, K. Y., Hu, X., ... & Johnson, J. D. (2012). Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. Cell metabolism, 16(6), 723-737.

Meneghini, L. (2020). Insulin-Dependent Diabetes Mellitus (IDDM). Encyclopedia of Behavioral Medicine, 1202-1203.

Miura, Y., Yasuda, R., Toma, N., & Suzuki, H. (2022). Non-Fasting Hypertriglyceridemia Burden as a Residual Risk of the Progression of Carotid Artery Stenosis. *International Journal of Molecular Sciences*, *23*(16), 9197.

Morán-Costoya, A., Proenza, A. M., Gianotti, M., Lladó, I., & Valle, A. (2021). Sex Differences in Nonalcoholic Fatty Liver Disease: Estrogen Influence on the Liver–Adipose Tissue Crosstalk. Antioxidants & Redox Signaling, 35(9), 753-774.

Moser, B., & Loetscher, P. (2001). Lymphocyte traffic control by chemokines. *Nature immunology*, *2*(2), 123-128.

Muoio, D. M., & Newgard, C. B. (2008). Molecular and metabolic mechanisms of insulin resistance and β-cell failure in type 2 diabetes. Nature reviews Molecular cell biology, 9(3), 193-205.

Natalucci, V., Virgili, E., Calcagnoli, F., Valli, G., Agostini, D., Zeppa, S. D., ... & Emili, R. (2021). Cancer Related Anemia: An Integrated Multitarget Approach and Lifestyle Interventions. Nutrients, 13(2), 482.

Nathan, D. M., Turgeon, H., & Regan, S. (2007). Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia, 50(11), 2239-2244.

National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. NIH publication, 01-3305.

Nauck, M. (2016). Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Diabetes, Obesity and Metabolism, 18(3), 203-216.

Neels, J. G., & Olefsky, J. M. (2006). Inflamed fat: what starts the fire?. The Journal of clinical investigation, 116(1), 33-35

Nibali, L., Gkranias, N., Mainas, G., & Di Pino, A. (2022). Periodontitis and implant complications in diabetes. Periodontology 2000.

O'Donnell, E., & O'Donnell, L. (2019). A Review of Type 1 Diabetes (T1D). Data Analytics in Medicine: Concepts, Methodologies, Tools, and Applications: Concepts, Methodologies, Tools, and Applications, 13.

Odell, W. D., Parlow, A. F., Swerdloff, R. S., Wabh, P. C., & Jacobs, H. S. (1981). Estimation of FSH test assay. Journal of clinical investigation, 47, 25-51.

Oku, A., Ueta, K., Arakawa, K., Ishihara, T., Nawano, M., Kuronuma, Y., ... & Endou, H. (1999). T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes. Diabetes, 48(9), 1794-1800.

Onge, E. S., Miller, S. A., Motycka, C., & DeBerry, A. (2015). A review of the treatment of type 2 diabetes in children. The Journal of Pediatric Pharmacology and Therapeutics, 20(1), 4-16.

Ozougwu, J. C., Obimba, K. C., Belonwu, C. D., & Unakalamba, C. B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol, 4(4), 46-57.

Ozougwu, J. C., Obimba, K. C., Belonwu, C. D., & Unakalamba, C. B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol, 4(4), 46-57.

Pamuk, F., & Kantarci, A. (2022). Inflammation as a link between periodontal disease and obesity. Periodontology 2000.

Panee, J. (2012). Monocyte Chemoattractant Protein 1 (MCP-1) in obesity and diabetes. Cytokine, 60(1), 1-12.

Park, K. G., Park, K. S., Kim, M. J., Kim, H. S., Suh, Y. S., Ahn, J. D., ... & Lee, I. K. (2004). Relationship between serum adiponectin and leptin concentrations and body fat distribution. Diabetes research and clinical practice, 63(2), 135-142.

Peng, Y. J., Shen, T. L., Chen, Y. S., Mersmann, H. J., Liu, B. H., & Ding, S. T. (2018). Adiponectin and adiponectin receptor 1 overexpression enhance inflammatory bowel disease. Journal of biomedical science, 25(1), 1-13.

Penney, A., Muhar, B. K., & Kotchoni, S. (2022). Biologics and Biosimilars Used for Diabetes. In Biologics and Biosimilars (pp. 269-280). CRC Press.

Periñán, M. T., Brolin, K., Bandres-Ciga, S., Blauwendraat, C., Klein, C., Gan-Or, Z., ... & Noyce, A. (2022). Effect modification between genes and environment, and Parkinson's disease risk. Annals of Neurology.

Broni, E. K., Ndumele, C. E., Echouffo-Tcheugui, J. B., Kalyani, R. R., Bennett, W. L., & Michos, E. D. (2022). The Diabetes-Cardiovascular Connection in Women: Understanding the Known Risks, Outcomes, and Implications for Care. Current diabetes reports, 1-15.

Murea, M., Ma, L., & Freedman, B. I. (2012). Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. The review of diabetic studies: RDS, 9(1), 6.

Bonnefond, A., Froguel, P., & Vaxillaire, M. (2010). The emerging genetics of type 2 diabetes. Trends in molecular medicine, 16(9), 407-416.

Perk, J. et al. 2012. "Erratum: 'European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012)' the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constit." European Heart Journal 33(17): 2126.

Picu, A., Petcu, L., Ştefan, S., Mitu, M., Lixandru, D., Ionescu-Tîrgovişte, C., ... & Chifiriuc, M. C. (2017). Markers of oxidative stress and antioxidant defense in romanian patients with type 2 diabetes mellitus and obesity. Molecules, 22(5), 714.

Piemonti, L., Calori, G., Lattuada, G., Mercalli, A., Ragogna, F., Garancini, M. P., ... & Perseghin, G. (2009). Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular disease mortality in middle-aged diabetic and nondiabetic individuals. Diabetes care, 32(11), 2105-2110.

Piemonti, L., Calori, G., Lattuada, G., Mercalli, A., Ragogna, F., Garancini, M. P., ... & Perseghin, G. (2009). Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular disease mortality in middle-aged diabetic and nondiabetic individuals. Diabetes care, 32(11), 2105-2110.

Pigeyre, M., & Meyre, D. (2018). Monogenic obesity. In Pediatric Obesity (pp. 135-152). Humana Press, Cham.

Pozo Garcia, L., Thomas, S. S., Rajesh, H., & Navaneethan, S. D. (2022). Progress in the management of patients with diabetes and chronic kidney disease. Current Opinion in Nephrology and Hypertension, 31(5), 456-463.

Prasad, M., Jayaraman, S., Eladl, M. A., El-Sherbiny, M., Abdelrahman, M. A. E., Veeraraghavan, V. P., ... & Rajagopal, P. (2022).

A Comprehensive review on therapeutic perspectives of phytosterols in insulin resistance: A mechanistic approach. Molecules, 27(5), 1595.

Ramesh, G., MacLean, A. G., & Philipp, M. T. (2013). Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediators of inflammation, 2013.

Razali, N., Aziz, A. A., Lim, C. Y., & Junit, S. M. (2015). Investigation into the effects of antioxidant-rich extract of Tamarindus indica leaf on antioxidant enzyme activities, oxidative stress and gene expression profiles in HepG2 cells. PeerJ, 3, e1292.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reese, J. M., Suman, V. J., Subramaniam, M., Wu, X., Negron, V., Gingery, A., ... & Hawse, J. R. (2014). ERβ1: characterization, prognosis, and evaluation of treatment strategies in ERα-positive and-negative breast cancer. BMC cancer, 14(1), 1-16.

Rega-Kaun, G., Kaun, C., & Wojta, J. (2013). More than a simple storage organ: adipose tissue as a source of adipokines involved in cardiovascular disease. Thrombosis and haemostasis, 110(10), 641-650.

Rhea, E. M., Banks, W. A., & Raber, J. (2022). Insulin Resistance in Peripheral Tissues and the Brain: A Tale of Two Sites. Biomedicines, 10(7), 1582.

Rogal, J., Zbinden, A., Schenke-Layland, K., & Loskill, P. (2019). Stem-cell based organ-on-a-chip models for diabetes research. Advanced Drug Delivery Reviews, 140, 101-128.

Rovin, B. H., & Song, H. (2006). Chemokine induction by the adipocyte-derived cytokine adiponectin. Clinical Immunology, 120(1), 99-105.

Ruderman, N., Chisholm, D., Pi-Sunyer, X., & Schneider, S. (1998). The metabolically obese, normal-weight individual revisited. Diabetes, 47(5), 699-713.

Saad, B., Kmail, A., & Haq, S. Z. (2022). Anti-Diabesity Middle Eastern Medicinal Plants and Their Action Mechanisms. Evidence-Based Complementary and Alternative Medicine, 2022.

Saad, B., Kmail, A., & Haq, S. Z. (2022). Anti-Diabesity Middle Eastern Medicinal Plants and Their Action Mechanisms. Evidence-Based Complementary and Alternative Medicine, 2022.

Sabanayagam, C., Sultana, R., Banu, R., Rim, T., Tham, Y. C., Mohan, S., ... & Jonas, J. B. (2021). Association between body mass index and diabetic retinopathy in Asians: the Asian Eye Epidemiology Consortium (AEEC) study. British Journal of Ophthalmology.

Sakers, A., De Siqueira, M. K., Seale, P., & Villanueva, C. J. (2022). Adipose-tissue plasticity in health and disease. Cell, 185(3), 419-446.

Salcedo, R., Ponce, M. L., Young, H. A., Wasserman, K., Ward, J. M., Kleinman, H. K., ... & Murphy, W. J. (2000). Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood, The Journal of the American Society of Hematology, 96(1), 34-40.

Saponaro, C., Gaggini, M., Carli, F., & Gastaldelli, A. (2015). The subtle balance between lipolysis and lipogenesis: a critical point in metabolic homeostasis. Nutrients, 7(11), 9453-9474.

Sarmadi, M., Ahmadi-Soleimani, S. M., Fararouei, M., & Dianatinasab, M. (2021). COVID-19, body mass index and cholesterol: an ecological study using global data. *BMC Public Health*, *21*(1), 1-14.

Sasaki, N., Maeda, R., Ozono, R., Yoshimura, K., Nakano, Y., & Higashi, Y. (2022). Early-Phase Changes in Serum Free Fatty Acid Levels After Glucose Intake Are Associated With Type 2 Diabetes Incidence: The Hiroshima Study on Glucose Metabolism and Cardiovascular Diseases. Diabetes Care.

Schäfer, K., Fujisawa, K., Konstantinides, S., & Loskutoff, D. J. (2001). Disruption of the plasminogen activator inhibitor-1 gene reduces the adiposity and improves the metabolic profile of genetically obese and diabetic ob/ob mice. The FASEB Journal, 15(10), 1840-1842.

Schaible, U. E., & Kaufmann, S. H. E. (2007). Malnutrition and infection: complex mechanisms and global impacts. *PLoS medicine*, *4*(5), e115.

Aleem S, Iqbal R, Shar T, Noreen S, Rafiq N, Javed I, et al. Complications of Diabetes: An Insight into Genetic Polymorphism and Role of Insulin. Recent patents on inflammation & allergy drug discovery. 2018;12(1):78-86.

Association AD. 14. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41(Supplement 1):S144-S51.

Association AD. Diagnosis and classification of diabetes mellitus Diabetes care. 2014;37(Supplement 1):S81-S90.

Classification and diagnosis of diabetes. Diabetes Care. American Diabetes Association. 2017;39(1):S13-S22.

Jin W, Patti M-E. Genetic determinants and molecular pathways in the pathogenesis of Type 2 diabetes. Clinical Science. 2009;116(2):99-111..

Kalia, V., & Pundir, C. S. (2004). Determination of serum triglycerides using lipase, glycerol kinase, glycerol-3-phosphate oxidase and peroxidase co-immobilized onto alkylamine glass beads.

Misra, K., Dhillon, G. S., Brar, S. K., & Verma, M. (2014). Antioxidants. In Biotransformation of waste biomass into high value biochemicals (pp. 117-138). Springer, New York, NY.

Molnár, D., Decsi, T., & Koletzko, B. (2004). Reduced antioxidant status in obese children with multimetabolic syndrome. International Journal of Obesity, 28(10), 1197-1202.

Scheel, A. K., Espelage, L., & Chadt, A. (2022). Many Ways to Rome: Exercise, Cold Exposure and Diet—Do They All Affect BAT Activation and WAT Browning in the Same Manner?. International Journal of Molecular Sciences, 23(9), 4759.

Scherer, P. E. (2006). Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes, 55(6), 1537-1545.

Scherer, P. E. (2016). The multifaceted roles of adipose tissue—therapeutic targets for diabetes and beyond: The 2015 Banting Lecture. Diabetes, 65(6), 1452-1461.

Schettler, G., & Nussel, E. (1975). Method for triglycerides. Aeb. Med. Soz. Med. Prav. Med, 10(25).

Shah, M. A., Haris, M., Faheem, H. I., Hamid, A., Yousaf, R., Rasul, A., ... & Althobaiti, N. A. (2022). Cross-Talk between Obesity and Diabetes: Introducing Polyphenols as an Effective Phytomedicine to Combat the Dual Sword Diabesity. Current Pharmaceutical Design.

Shahwan, M., Alhumaydhi, F., Ashraf, G. M., Hasan, P. M., & Shamsi, A. (2022). Role of polyphenols in combating Type 2 Diabetes and insulin resistance. International Journal of Biological Macromolecules.

Shahwan, M., Alhumaydhi, F., Ashraf, G. M., Hasan, P. M., & Shamsi, A. (2022). Role of polyphenols in combating Type 2 Diabetes and insulin resistance. International Journal of Biological Macromolecules.

Sharma, D., Arora, S., Banerjee, A., & Singh, J. (2021). Improved insulin sensitivity in obese-diabetic mice via chitosan Nanomicelles

mediated silencing of pro-inflammatory Adipocytokines. Nanomedicine: Nanotechnology, Biology and Medicine, 33, 102357.

Shaw ND, Srouji SS, Histed SN, et al. Aging attenuates the pituitary response to gonadotropin-releasing hormone. J Clin Endocrinol Metab 2009;94:3259–64

Shaw, N. D., Histed, S. N., Srouji, S. S., Yang, J., Lee, H., & Hall, J. E. (2010). Estrogen negative feedback on gonadotropin secretion: evidence for a direct pituitary effect in women. The Journal of Clinical Endocrinology & Metabolism, 95(4), 1955-1961.

Singh, S., Anshita, D., & Ravichandiran, V. (2021). MCP-1: Function, regulation, and involvement in disease. *International immunopharmacology*, *101*, 107598.

SKONIECZNA-ŻYDECKA, K., PALMA, J., ŁONIEWSKI, I., & STACHOWSKA, E. (2021). I. SZYDŁOWSKA1, A. MARCINIAK1, A. BRODOWSKA1, B. LOJ2, S. CIEĆWIEŻ1. European Review for Medical and Pharmacological Sciences, 25, 3859-3867.

Snijder, M. B., Heine, R. J., Seidell, J. C., Bouter, L. M., Stehouwer, C. D., Nijpels, G., ... & Dekker, J. M. (2006). Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the hoorn study. Diabetes care, 29(11), 2498-2503.

Sobczak, Amélie IS, and Alan J. Stewart. "Coagulatory defects in type-1 and type-2 diabetes." International journal of molecular sciences 20.24 (2019): 6345.

Stanimirovic, J., Radovanovic, J., Banjac, K., Obradovic, M., Essack, M., Zafirovic, S., ... & Isenovic, E. R. (2022). Role of C-Reactive Protein in Diabetic Inflammation. Mediators of Inflammation, 2022.

Stefanska, A., Ponikowska, I., Cwiklinska-Jurkowska, M., & Sypniewska, G. (2014). Association of FSH with metabolic syndrome in postmenopausal women: a comparison with CRP, adiponectin and leptin. Biomarkers in medicine, 8(7), 921-930.

Stefanska, A., Sypniewska, G., Ponikowska, I., & Cwiklinska-Jurkowska, M. (2012). Association of follicle-stimulating hormone and

sex hormone binding globulin with the metabolic syndrome in postmenopausal women. Clinical biochemistry, 45(9), 703-706.

Suleiman, M., Marselli, L., Cnop, M., Eizirik, D. L., De Luca, C., Femia, F. R., ... & Marchetti, P. (2022). The Role of Beta Cell Recovery in Type 2 Diabetes Remission. International journal of molecular sciences, 23(13), 7435.

Takahashi, M., Yamamuro, D., Wakabayashi, T., Takei, A., Takei, S., Nagashima, S., ... & Ishibashi, S. (2022). Loss of myeloid lipoprotein lipase exacerbates adipose tissue fibrosis with collagen VI deposition and hyperlipidemia in leptin-deficient obese mice. Journal of Biological Chemistry, 102322.

Taylor, A. E., McCourt, B., Martin, K. A., Anderson, E. J., Adams, J. M., Schoenfeld, D., & Hall, J. E. (1997). Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. The journal of clinical endocrinology & metabolism, 82(7), 2248-2256.

Thompson, K. A., & Kanamarlapudi, V. (2013). Type 2 diabetes mellitus and glucagon like peptide-1 receptor signalling. Clinical & Experimental Pharmacology, 3(04).

Thompson, K. A., & Kanamarlapudi, V. (2013). Type 2 diabetes mellitus and glucagon like peptide-1 receptor signalling. Clinical & Experimental Pharmacology, 3(04).

Thorne, S., Paterson, B., & Russell, C. (2003). The structure of everyday self-care decision making in chronic illness. Qualitative health research, 13(10), 1337-1352.

Toth, P. P., Barter, P. J., Rosenson, R. S., Boden, W. E., Chapman, M. J., Cuchel, M., ... & Rader, D. J. (2013). High-density lipoproteins: a consensus statement from the National Lipid Association. Journal of clinical lipidology, 7(5), 484-525.

Tricò, D., McCollum, S., Samuels, S., Santoro, N., Galderisi, A., Groop, L., ... & Shabanova, V. (2022). Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach. Diabetes care, 45(8), 1841-1851.

Tricò, D., McCollum, S., Samuels, S., Santoro, N., Galderisi, A., Groop, L., ... & Shabanova, V. (2022). Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach. Diabetes care, 45(8), 1841-1851.

Tricò, D., McCollum, S., Samuels, S., Santoro, N., Galderisi, A., Groop, L., ... & Shabanova, V. (2022). Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach. Diabetes care, 45(8), 1841-1851.

Tripathi, B. K., & Srivastava, A. K. (2006). Diabetes mellitus: complications and therapeutics. Med Sci Monit, 12(7), 130-47.

Trujillo-Viera, J., El-Merahbi, R., Schmidt, V., Karwen, T., Loza-Valdes, A., Strohmeyer, A., ... & Sumara, G. (2021). Protein Kinase D2 drives chylomicron-mediated lipid transport in the intestine and promotes obesity. EMBO molecular medicine, 13(5), e13548.

Tsatsanis, C., Zacharioudaki, V., Androulidaki, A., Dermitzaki, E., Charalampopoulos, I., Minas, V., ... & Margioris, A. N. (2005). Adiponectin induces TNF-α and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. Biochemical and biophysical research communications, 335(4), 1254-1263.

Van Arensbergen, J., García-Hurtado, J., Moran, I., Maestro, M. A., Xu, X., Van de Casteele, M., ... & Ferrer, J. (2010). Derepression of Polycomb targets during pancreatic organogenesis allows insulin-producing beta-cells to adopt a neural gene activity program. Genome research, 20(6), 722-732.

van Duinkerken, E., & Ryan, C. M. (2020). Diabetes mellitus in the young and the old: Effects on cognitive functioning across the life span. Neurobiology of disease, 134, 104608.

Van Greevenbroek, M. M., Schalkwijk, C. G., & Stehouwer, C. D. (2013). Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. Neth J Med, 71(4), 174-87.

Visser, J. A., de Jong, F. H., Laven, J. S., & Themmen, A. P. (2006). Anti-Mullerian hormone: a new marker for ovarian function. Reproduction, 131(1), 1-9.

WALDSTREICHER, J., SANTORO, N. F., HALL, J. E., FILICORI, M., & CROWLEY JR, W. F. (1988). Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: indirect evidence for partial gonadotroph desensitization. The Journal of Clinical Endocrinology & Metabolism, 66(1), 165-172.

Walz, A., Peveri, P., Aschauer, H., & Baggiolini, M. (1987). Purification and amino acid sequencing of NAF, a novel neutrophil-activating factor produced by monocytes. Biochemical and biophysical research communications, 149(2), 755-761.

Wang, N., Kuang, L., Han, B., Li, Q., Chen, Y., Zhu, C., ... & Lu, Y. (2016). Follicle-stimulating hormone associates with prediabetes and diabetes in postmenopausal women. Acta diabetologica, 53(2), 227-236.

Wang, X., Chen, C., Xie, C., Huang, W., Young, R. L., Jones, K. L., ... & Wu, T. (2022). Serum bile acid response to oral glucose is attenuated in patients with early type 2 diabetes and correlates with 2-hour plasma glucose in individuals without diabetes. Diabetes, Obesity and Metabolism, 24(6), 1132-1142.

Weykamp, C. (2013). HbA1c: a review of analytical and clinical aspects. Annals of laboratory medicine, 33(6), 393.

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., & Ferrante, A. W. (2003). Obesity is associated with macrophage accumulation in adipose tissue. The Journal of clinical investigation, 112(12), 1796-1808.

Weng, J., Ji, L., Jia, W., Lu, J., Zhou, Z., Zou, D., ... & Chinese Diabetes Society. (2016). Standards of care for type 2 diabetes in China. Diabetes/metabolism research and reviews, 32(5), 442.

WHO Expert Consultation Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–163.

Wild, S. H., & Byrne, C. D. (2013). Commentary: Sub-types of diabetes—what's new and what's not. International journal of epidemiology, 42(6), 1600-1602.

Wilding, J. (2014). The importance of weight management in type 2 diabetes mellitus. International journal of clinical practice, 68(6), 682-691.

Xue, D., Zheng, Y., Wen, J., Han, J., Tuo, H., Liu, Y., & Peng, Y. (2021). Role of chemokines in hepatocellular carcinoma. *Oncology Reports*, *45*(3), 809-823.

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007; 13: 332–339.

Yamauchi, T., & Kadowaki, T. (2008). Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. International journal of obesity, 32(7), S13-S18

Yamauchi, T., Iwabu, M., Okada-Iwabu, M., & Kadowaki, T. (2014). Adiponectin receptors: a review of their structure, function and how they work. Best practice & research Clinical endocrinology & metabolism, 28(1), 15-23.

Yazdanpanah, S., Rabiee, M., Tahriri, M., Abdolrahim, M., & Tayebi, L. (2015). Glycated hemoglobin-detection methods based on electrochemical biosensors. TrAC Trends in Analytical Chemistry, 72, 53-67.

Ye, J. (2013). Mechanisms of insulin resistance in obesity. Frontiers of medicine, 7(1), 14-24.

Yoshimura, T., Matsushima, K., Oppenheim, J. J., & Leonard, E. J. (1987). Neutrophil chemotactic factor produced by lipopolysaccharide (LPS)-stimulated human blood mononuclear leukocytes: partial characterization and separation from interleukin 1 (IL 1). The Journal of Immunology, 139(3), 788-793.

Zhang, S., Huang, Y. P., Li, J., Wang, W. H., Zhang, M. Y., Wang, X. C., ... & Li, C. J. (2022). The Visceral-Fat-Area-to-Hip-Circumference Ratio as a Predictor for Insulin Resistance in a Chinese Population with Type 2 Diabetes. Obesity Facts, 1-8.

Zhang, Z., Du, J., Shi, H., Wang, S., Yan, Y., Xu, Q., ... & Li, F. (2022). Adiponectin suppresses tumor growth of nasopharyngeal

carcinoma through activating AMPK signaling pathway. Journal C. M. Diaz-Melean, V. K. Somers, and J. P. Rodriguez-Escudero, “Mechanisms of adverse cardiometabolic consequences of obesity,” Current Atherosclerosis Reports, vol. 15, no. 11, p. 364, 2013.

Zhou, Y., & Xu, B. (2022). New insights into anti-diabetes effects and molecular mechanisms of dietary saponins. Critical Reviews in Food Science and Nutrition, 1-26.

Zhu, B., Li, Y., Mei, W., He, M., Ding, Y., Meng, B., ... & Xiang, G. (2019). Alogliptin improves endothelial function by promoting autophagy in perivascular adipose tissue of obese mice through a GLP-1-dependent mechanism. Vascular pharmacology, 115, 55-63.

Reference

Abdul-Ghani, M. A., Tripathy, D., & DeFronzo, R. A. (2006). Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes care, 29(5), 1130-1139.

Abou-Samra, M., Selvais, C. M., Dubuisson, N., & Brichard, S. M. (2020). Adiponectin and its mimics on skeletal muscle: insulin sensitizers, fat burners, exercise mimickers, muscling pills… or everything together?. International journal of molecular sciences, 21(7), 2620

Adnan, M. T., Amin, M. N., Uddin, M. G., Hussain, M. S., Sarwar, M. S., Hossain, M. K., ... & Islam, M. S. (2019). Increased concentration of serum MDA, decreased antioxidants and altered trace elements and macro-minerals are linked to obesity among Bangladeshi population. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(2), 933-938.

Adorni, M. P., Ronda, N., Bernini, F., & Zimetti, F. (2021). High density lipoprotein cholesterol efflux capacity and atherosclerosis in cardiovascular disease: pathophysiological aspects and pharmacological perspectives. *Cells*, *10*(3), 574.

Aguayo-Mazzucato, C. (2020). Functional changes in beta cells during ageing and senescence. *Diabetologia*, *63*(10), 2022-2029.

Ahuja, R. P., Fletcher, J. M., Granger, L. A., Liu, C. C., Miessler, B., & Mitchell, M. A. (2022). Changes in glucose tolerance and insulin secretion in a cohort of cats with chronic obesity. *Canadian Journal of Veterinary Research*, *86*(3), 181-187.

Al Yafi, M., Nasif, A., Glosser, L. D., Ren, G., Ahemd, A., Nazzal, M., & Osman, M. (2022). The relationship between lower extremity amputation and body mass index. Vascular, 17085381221087824.

Al-Ameri, A. A., & AM AL-Mashhedy, L. (2021). The Association between Lipocalin 2 and obesity for diabetic Female Type II. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO, 8805-8814.

Al-Azemi, M., Omu, F. E., & Omu, A. E. (2004). The effect of obesity on the outcome of infertility management in women with polycystic ovary syndrome. Archives of gynecology and obstetrics, 270(4), 205-210.

Alberti, K. G. M. M., Zimmet, P., & Shaw, J. (2007). International Diabetes Federation: a consensus on Type 2 diabetes prev ention. Diabetic Medicine, 24(5), 451-463.

Ali, N. (2011). Diabetes and you: A comprehensive, holistic approach. Rowman & Littlefield Publishers.

Alipio, Z., Liao, W., Roemer, E. J., Waner, M., Fink, L. M., Ward, D. C., & Ma, Y. (2010). Reversal of hyperglycemia in diabetic mouse models using induced-pluripotent stem (iPS)-derived pancreatic β-like cells. Proceedings of the National Academy of Sciences, 107(30), 13426-13431.

Alizadeh, H. (2022). Meteorin-like protein (Metrnl): A metabolic syndrome biomarker and an exercise mediator. Cytokine, 157, 155952.

Almubarak, F. (2016). The Association Between Known Risk Factors for Type 2 Diabetes, and the Body Mass Index of Diabetic Adults. University of Arkansas.

Aluganti Narasimhulu, C., & Parthasarathy, S. (2022). Preparation of LDL, Oxidation, Methods of Detection, and Applications in Atherosclerosis Research. In Atherosclerosis (pp. 213-246). Humana, New York, NY.

American Diabetes Association. (2014). Diagnosis and classification of diabetes mellitus. Diabetes care, 37(Supplement_1), S81-S90.

Amin, M. N., Liza, K. F., Sarwar, M., Ahmed, J., Adnan, M., Chowdhury, M. I., ... & Islam, M. S. (2015). Effect of lipid peroxidation, antioxidants, macro minerals and trace elements on eczema. Archives of dermatological research, 307(7), 617-623.

Amirkhizi, Farshad, Fereydoun Siassi, Mahmoud Djalali, and Abbas Rahimi Foroushani. 2010. “Evaluation of Oxidative Stress and Total Antioxidant Capacity in Women with General and Abdominal Adiposity.”

Obesity Research and Clinical Practice 4(3): e209–16. http://dx.doi.org/10.1016/j.orcp.2010.02.003.

Anandasundaram, B., Lane, D. A., Apostolakis, S., & Lip, G. Y. H. (2013). The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. Journal of Thrombosis and Haemostasis, 11(5), 975-987.

Andreadi, A., Bellia, A., Di Daniele, N., Meloni, M., Lauro, R., Della-Morte, D., & Lauro, D. (2022). The molecular link between oxidative stress, insulin resistance, and type 2 diabetes: A target for new therapies against cardiovascular diseases. Current Opinion in Pharmacology, 62, 85-96.

Anzueto, A., Frutos-Vivar, F., Esteban, A., Bensalami, N., Marks, D., Raymondos, K., ... & Ferguson, N. D. (2011). Influence of body mass index on outcome of the mechanically ventilated patients. Thorax, 66(1), 66-73.

Apak, Reşat et al. 2005. "Total Antioxidant Capacity Assay of Human Serum Using Copper(II)-Neocuproine as Chromogenic Oxidant: The CUPRAC Method." Free Radical Research 39(9): 949–61.

Arakelyan, A., Petrkova, J., Hermanova, Z., Boyajyan, A., Lukl, J., & Petrek, M. (2005). Serum levels of the MCP-1 chemokine in patients with ischemic stroke and myocardial infarction. Mediators of inflammation, 2005(3), 175-179.

Ardisson Korat, A. V., Willett, W. C., & Hu, F. B. (2014). Diet, lifestyle, and genetic risk factors for type 2 diabetes: a review from the Nurses' Health Study, Nurses' Health Study 2, and Health Professionals' Follow-up Study. Current nutrition reports, 3(4), 345-354.

Artham, S. M., Lavie, C. J., Milani, R. V., & Ventura, H. O. (2008). The obesity paradox: impact of obesity on the prevalence and prognosis of cardiovascular diseases. Postgraduate medicine, 120(2), 34-41.

Asif, M. (2014). The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. Journal of education and health promotion, 3.

Association, A. D. (2001). Hyperglycemic crises in patients with diabetes mellitus. Diabetes Care, 24(1), 154-161.

Astrup, A. (2001). Healthy lifestyles in Europe: prevention of obesity and type II diabetes by diet and physical activity. Public health nutrition, 4(2b), 499-515.

Bagdade, J. D., Bierman, E. L., & Porte, D. (1967). The significance of basal insulin levels in the evaluation of the insulin response to glucose in diabetic and nondiabetic subjects. The Journal of clinical investigation, 46(10), 1549-1557.

Bailey, C. J. (2017). Metformin: historical overview. Diabetologia, 60(9), 1566-1576.

Banerjee, A., Pathak, S., & Duttaroy, A. K. (2022). Dietary Fats and the Gut Microbiota: Their impacts on lipid-induced metabolic syndrome. Journal of Functional Foods, 91, 105026.

Barham, Denise, and P. Trinder. 1972. "An Improved Colour Reagent for the Determination of Blood Glucose by the Oxidase System." The Analyst 97(1151): 142–45.

Berman, C., Naguib, M., Hegedus, E., & Vidmar, A. P. (2022). Topiramate for Weight Management in Children with Severe Obesity. Childhood Obesity.

Bhandari, M., Kosta, S., Bhandari, M., Reddy, M., Mathur, W., & Gupta, M. (2022). Effects of Bariatric Surgery on People with Obesity and Polycystic Ovary Syndrome: a Large Single Center Study from India. Obesity Surgery, 1-8.

Bhatti, J. S., Sehrawat, A., Mishra, J., Sidhu, I. S., Navik, U., Khullar, N., ... & Reddy, P. H. (2022). Oxidative stress in the pathophysiology of type 2 diabetes and related complic ations: Current therapeutics strategies and future perspectives. Free Radical Biology and Medicine.

Bhatti, M. S., Akbri, M. Z. A., & Shakoor, M. (2001). Lipid profile in obesity. *Journal of Ayub Medical College Abbottabad*, *13*(1), 31-33.

Bilgili, S., Celebiler, A. C., Dogan, A., & Karaca, B. (2008). Inverse relationship between adiponectin and plasminogen activator inhibitor-1 in metabolic syndrome patients. Endocrine regulations, 42(2-3), 63-68.

Bishop, C. W., Strugnell, S. A., Csomor, P., Kaiser, E., & Ashfaq, A. (2022). Extended-Release Calcifediol Effectively Raises Serum Total 25-Hydroxyvitamin D Even in Overweight Nondialysis Chronic Kidney Disease Patients with Secondary Hyperparathyroidism. American Journal of Nephrology, 1-9.

Blüher, M. (2019). Obesity: global epidemiology and pathogenesis. Nature Reviews Endocrinology, 15(5), 288-298.

Boland, B. B., Rhodes, C. J., & Grimsby, J. S. (2017). The dynamic plasticity of insulin production in β-cells. Molecular metabolism, 6(9), 958-973.

Boyle, J. P., Thompson, T. J., Gregg, E. W., Barker, L. E., & Williamson, D. F. (2010). Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Population health metrics, 8(1), 1-12.

Bozkurt, S., Coskun, H., Kadioglu, H., Memmi, N., Cipe, G., Ersoy, Y. E., ... & Muslumanoglu, M. (2013). Remission of ulcerated necrobiosis lipoidica diabeticorum after bariatric surgery. Case Reports in Dermatological Medicine, 2013.

Braoudaki, M., Ahmad, M. S., Mustafov, D., Seriah, S., Siddiqui, M. N., & Siddiqui, S. S. (2022, June). Chemokines and chemokine receptors in colorectal cancer; multifarious roles and clinical impact. In Seminars in Cancer Biology. Academic Press.

Brehm, A., Krssak, M., Schmid, A. I., Nowotny, P., Waldhäusl, W., & Roden, M. (2006). Increased lipid availability impairs insulin-stimulated ATP synthesis in human skeletal muscle. Diabetes, 55(1), 136-140.

Carchman, R. M., Dechert-Zeger, M., Calikoglu, A. S., & Harris, B. D. (2005). A new challenge in pediatric obesity: pediatric hyperglycemic hyperosmolar syndrome. Pediatric Critical Care Medicine, 6(1), 20-24.

Carmichael, L., Keske, M. A., Betik, A. C., Parker, L., Brayner, B., Roberts-Thomson, K. M., ... & Kaur, G. (2022). Is vascular insulin

resistance an early step in diet-induced whole-body insulin resistance?. Nutrition & Diabetes, 12(1), 1-12.

Chandi, M. (2018). Inhibition of insulin secretion in β-cells exposed to arsenic, cadmium and manganese is associated with altered microRNA expression.

Chaudhury, A., Duvoor, C., Reddy Dendi, V. S., Kraleti, S., Chada, A., Ravilla, R., ... & Mirza, W. (2017). Clinical review of antidiabetic drugs: implications for type 2 diabetes mellitus management. Frontiers in endocrinology, 8, 6.

Chen, L., Magliano, D. J., & Zimmet, P. Z. (2012). The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nature reviews endocrinology, 8(4), 228-236.

Chen, X., Wang, K., Lu, T., Wang, J., Zhou, T., Tian, J., ... & Zhou, Q. (2022). Adiponectin is negatively associated with disease activity and Sharp score in treatment-naïve Han Chinese rheumatoid arthritis patients. Scientific reports, 12(1), 1-7.

Cherrington, A. D. (1999). Banting Lecture 1997. Control of glucose uptake and release by the liver in vivo. Diabetes, 48(5), 1198-1214.

Cho, N. H., Ku, E. J., Jung, K. Y., Oh, T. J., Kwak, S. H., Moon, J. H., ... & Choi, S. H. (2020). Estimated association between cytokines and the progression to diabetes: 10-year follow-up from a community-based cohort. The Journal of Clinical Endocrinology & Metabolism, 105(3), e381-e389.

Choi, J. W., Han, E., & Kim, T. H. (2022). Risk of Hypertension and Type 2 Diabetes in Relation to Changes in Alcohol Consumption: A Nationwide Cohort Study. International Journal of Environmental Research and Public Health, 19(9), 4941.

Choi, J. Y., Shin, J., & Baek, S. (2021). Gender-based comparison of factors affecting regular exercise of patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) based on the 7th Korea National Health and Nutrition Examination Survey (KNHANES). Plos one, 16(9), e0257822.

Choi, S. H., Hong, E. S., & Lim, S. (2013). Clinical implications of adipocytokines and newly emerging metabolic factors with relation to

insulin resistance and cardiovascular health. Frontiers in endocrinology, 4, 97.

Chung, W. K. (2012). An overview of mongenic and syndromic obesities in humans. Pediatric blood & cancer, 58(1), 122-128.

Cioana, M., Deng, J., Hou, M., Nadarajah, A., Qiu, Y., Chen, S. S. J., ... & Samaan, M. C. (2021). Prevalence of hypertension and albuminuria in pediatric type 2 diabetes: a systematic review and meta-analysis. JAMA network open, 4(4), e216069-e216069.

Cioana, M., Deng, J., Hou, M., Nadarajah, A., Qiu, Y., Chen, S. S. J., ... & Samaan, M. C. (2021). Prevalence of hypertension and albuminuria in pediatric type 2 diabetes: a systematic review and meta-analysis. JAMA network open, 4(4), e216069-e216069.

Cnop, M., Havel, P. J., Utzschneider, K. M., Carr, D. B., Sinha, M. K., Boyko, E. J., ... & Kahn, S. E. (2003). Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia, 46(4), 459-469.

Cohen, K. E., Katunaric, B., Schulz, M. E., SenthilKumar, G., Young, M. S., Mace, J. E., & Freed, J. K. (2022). Role of Adiponectin Receptor 1 in Promoting Nitric Oxide-Mediated Flow-Induced Dilation in the Human Microvasculature. Frontiers in Pharmacology, 13, 875900.

Cottam, D. R., Mattar, S. G., Barinas-Mitchell, E., Eid, G., Kuller, L., Kelley, D. E., & Schauer, P. R. (2004). The chronic inflammatory hypothesis for the morbidity associated with morbid obesity: implications and effects of weight loss. Obesity surgery, 14(5), 589-600.

Cox, C. L., Stanhope, K. L., Schwarz, J. M., Graham, J. L., Hatcher, B., Griffen, S. C., ... & Havel, P. J. (2011). Circulating concentrations of monocyte chemoattractant protein-1, plasminogen activator inhibitor-1, and soluble leukocyte adhesion molecule-1 in overweight/obese men and women consuming fructose-or glucose-sweetened beverages for 10 weeks. The Journal of Clinical Endocrinology & Metabolism, 96(12), E2034-E2038.

Cui, H., Zhao, G., Liu, R., Zheng, M., Chen, J., & Wen, J. (2012). FSH stimulates lipid biosynthesis in chicken adipose tissue by upregulating the expression of its receptor FSHR. Journal of lipid research, 53(5), 909-917.

Cui, X., Feng, J., Wei, T., Gu, L., Wang, D., Lang, S., ... & Hong, T. (2022). Pro-α-cell-derived β-cells contribute to β-cell neogenesis induced by antagonistic glucagon receptor antibody in type 2 diabetic mice. Iscience, 25(7), 104567.

Cushing, S. D., Berliner, J. A., Valente, A. J., Territo, M. C., Navab, M., Parhami, F., ... & Fogelman, A. M. (1990). Minimally modified low density lipoprotein induces monocyte chemotactic protein 1 in human endothelial cells and smooth muscle cells. Proceedings of the National Academy of Sciences, 87(13), 5134-5138.

Cusi, K., & DeFronzo, R. A. (1998). Metformin: a review of its metabolic effects. Diabetes Reviews, 6(2), 89-131.

Dart, A. (2010). The natural history of youth onset type 2 diabetes mellitus. University of Manitoba (Canada)….

de Wit, A. E. (2021). From academia to society–improving the quality of science journalism. Can hormones get you down?, 223.

DeFronzo, R. A., Eldor, R., & Abdul-Ghani, M. (2013). Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes care, 36(Supplement_2), S127-S138.

Delaney, M. F., Zisman, A., & Kettyle, W. M. (2000). Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinology and metabolism clinics of North America, 29(4), 683-705.

Deshmane, S. L., Kremlev, S., Amini, S., & Sawaya, B. E. (2009). Monocyte chemoattractant protein-1 (MCP-1): an overview. Journal of interferon & cytokine research, 29(6), 313-326.

Després, J. P., & Lemieux, I. (2006). Abdominal obesity and metabolic syndrome. Nature, 444(7121), 881-887.

Devi, L. A. (2000). G-protein-coupled receptor dimers in the lime light. Trends in Pharmacological Sciences, 21(9), 324-326.

Domínguez, F., & Alonso-Castro, Á. (2022). Adipokines, Possible Biomarkers and Therapeutic Targets in Obesity and Related Pathologies. Diabesity: A Multidisciplinary Approach, 58.

Du, A. L., Tully, J. L., Curran, B. P., & Gabriel, R. A. (2022). Obesity and outcomes in patients undergoing upper airway surgery for obstructive sleep apnea. PloS one, 17(8), e0272331.

Duncombe, S. L., Barker, A. R., Bond, B., Earle, R., Varley-Campbell, J., Vlachopoulos, D., ... & Stylianou, M. (2022). School-based high-intensity interval training programs in children and adolescents: A systematic review and meta-analysis. *PloS one*, *17*(5), e0266427.

Dyslipidemia, H. (2014). 10 Vascular Biology of Atherosclerosis in Patients with Diabetes. Diabetes in Cardiovascular Disease: A Companion to Braunwald's Heart Disease E-Book, 7, 111.

Elena, P., Päivi, H., Heini, H., & Saara, M. (2022). Glycaemic control in insulin deficient patients using different insulin delivery and glucose sensoring devices: cross-sectional real-life study. Diabetes Epidemiology and Management, 100072.

Enas R, A. H., Azza A, A. S., Rania N, S., Eman R, Y., Mones M, A. S., Amr Said, M., & Nadia A, M. (2015). Serum levels of monocyte chemoattractant protein-1, interlukin-6, and paraoxonase-1 in childhood obesity.

Erel, Ozcan. 2005. "A New Automated Colorimetric Method for Measuring Total Oxidant Status." Clinical Biochemistry 38(12): 1103–11.

Ervin, R. B. (2009). Prevalence of metabolic syndrome among adults 20 years of age and over, by sex, age, race and ethnicity, and body mass index: United States, 2003-2006.

Fanchin, R., Taieb, J., Lozano, D. H. M., Ducot, B., Frydman, R., & Bouyer, J. (2005). High reproducibility of serum anti-Müllerian hormone measurements suggests a multi-staged follicular secretion and strengthens its role in the assessment of ovarian follicular status. Human Reproduction, 20(4), 923-927.

Farooqi, I. S., & O Rahilly, S. (2004). Monogenic human obesity syndromes. Recent progress in hormone research, 59, 409-424.

Fenske, B., Kische, H., Gross, S., Wallaschofski, H., Völzke, H., Dörr, M., ... & Haring, R. (2015). Endogenous androgens and sex hormone–binding globulin in women and risk of metabolic syndrome and type 2 diabetes. The Journal of Clinical Endocrinology & Metabolism, 100(12), 4595-4603.

Fernández-Millán, E., & Guillén, C. (2022). Multi-organ crosstalk with endocrine pancreas: A focus on how gut microbiota shapes pancreatic Beta-cells. Biomolecules, 12(1), 104.

Ferreira, V. L., Borba, H. H., Bonetti, A. D. F., Leonart, L., & Pontarolo, R. (2018). Cytokines and interferons: types and functions. *Autoantibodies and cytokines*, *13*.

Fonseca, V. A. (2009). Defining and characterizing the progression of type 2 diabetes. Diabetes care, 32(suppl 2), S151-S156.

Fowler, M. J. (2008). Microvascular and macrovascular complications of diabetes. Clinical diabetes, 26(2), 77-82.

Freitas Lima, L. C., Braga, V. D. A., do Socorro de França Silva, M., Cruz, J. D. C., Sousa Santos, S. H., de Oliveira Monteiro, M. M., & Balarini, C. D. M. (2015). Adipokines, diabetes and atherosclerosis: an inflammatory association. *Frontiers in physiology*, *6*, 304.

Fried, S. K., Bunkin, D. A., & Greenberg, A. S. (1998). Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. The Journal of Clinical Endocrinology & Metabolism, 83(3), 847-850.

Fruchart, J. C., Sacks, F., Hermans, M. P., Assmann, G., Brown, W. V., Ceska, R., ... & Residual Risk Reduction Initiative. (2008). The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. The American journal of cardiology, 102(10), 1K-34K.

Frühbeck, G., & Salvador, J. (2004). Role of adipocytokines in metabolism and disease. *Nutrition Research*, *24*(10), 803-826.

Fujioka, K. (2005). Follow-up of nutritional and metabolic problems after bariatric surgery. Diabetes care, 28(2), 481-484.

Gambineri, A., Pelusi, C., Vicennati, V., Pagotto, U., & Pasquali, R. (2002). Obesity and the polycystic ovary syndrome. International journal of obesity, 26(7), 883-896.

Garg, M. K., Dutta, M. K., & Mahalle, N. (2012). Adipokines (adiponectin and plasminogen activator inhhibitor-1) in metabolic syndrome. Indian journal of endocrinology and metabolism, 16(1), 116.

Gastaldelli, A., Gaggini, M., & DeFronzo, R. A. (2017). Role of adipose tissue insulin resistance in the natural history of type 2 diabetes: results from the San Antonio Metabolism Study. Diabetes, 66(4), 815-822.

Gavin, K. M., & Bessesen, D. H. (2020). Sex differences in adipose tissue function. *Endocrinology and Metabolism Clinics*, *49*(2), 215-228.

Geng, S., Chen, K., Yuan, R., Peng, L., Maitra, U., Diao, N., ... & Li, L. (2016). The persistence of low-grade inflammatory monocytes contributes to aggravated atherosclerosis. Nature communications, 7(1), 1-15.

Genuth, S. (1992). Management of the adult onset diabetic with sulfonylurea drug failure. Endocrinology and metabolism clinics of North America, 21(2), 351-370.

Gheitasi, I., Savari, F., Akbari, G., Mohammadi, J., Fallahzadeh, A. R., & Sadeghi, H. (2022). Molecular Mechanisms of Hawthorn Extracts in Multiple Organs Disorders in Underlying of Diabetes: A Review. International Journal of Endocrinology, 2022.

Golay, A., & Ybarra, J. (2005). Link between obesity and type 2 diabetes. Best practice & research Clinical endocrinology & metabolism, 19(4), 649-663.

Goldstein, D. P., & Kosasa, T. S. (1975). The subunit radioimmunoassay for hCG-Clinical application. Progress in Gynecology, 6, 145-184.

Gonzalez, L. L., Garrie, K., & Turner, M. D. (2018). Type 2 diabetes–an autoinflammatory disease driven by metabolic stress. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1864(11), 3805-3823.

Gordon, T., Castelli, W. P., Hjortland, M. C., Kannel, W. B., & Dawber, T. R. (1977). High density lipoprotein as a protective factor against coronary heart disease: the Framingham Study. The American journal of medicine, 62(5), 707-714.

Gou, W., Ling, C. W., He, Y., Jiang, Z., Fu, Y., Xu, F., ... & Zheng, J. S. (2021). Interpretable machine learning framework reveals robust gut microbiome features associated with type 2 diabetes. Diabetes Care, 44(2), 358-366.

Grant, P. J. (2007). Diabetes mellitus as a prothrombotic condition. Journal of internal medicine, 262(2), 157-172.

Greenberg, A. S., & Obin, M. S. (2006). Obesity and the role of adipose tissue in inflammation and metabolism. The American journal of clinical nutrition, 83(2), 461S-465S.

Griffin, M. J. (2022). On the Immunometabolic Role of NF-κB in Adipocytes. Immunometabolism, 4(1).

Guariguata, L., Whiting, D. R., Hambleton, I., Beagley, J., Linnenkamp, U., & Shaw, J. E. (2014). Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice, 103(2), 137-149.

Guillausseau, P. J., Meas, T., Virally, M., Laloi-Michelin, M., Médeau, V., & Kevorkian, J. P. (2008). Abnormalities in insulin secretion in type 2 diabetes mellitus. Diabetes & metabolism, 34, S43-S48.

Gungor, N., Thompson, T., Sutton-Tyrrell, K., Janosky, J., & Arslanian, S. (2005). Early signs of cardiovascular disease in youth with obesity and type 2 diabetes. Diabetes care, 28(5), 1219-1221.

Guo, F., Moellering, D. R., & Garvey, W. T. (2014). Use of HbA1c for diagnoses of diabetes and prediabetes: comparison with diagnoses

based on fasting and 2-hr glucose values and effects of gender, race, and age. Metabolic syndrome and related disorders, 12(5), 258-268.

Gupta, P., & Gupta, S. (2016). Evaluation of Lipid Profile in Type-II Diabetes Mellitus with Obesity. jouranl of midical scince and clinical Research ,88(5), 2455-0450.

Hallenborg, P., Jensen, B. A. H., Fjære, E., Petersen, R. K., Belmaâti, M. S., Rasmussen, S. S., ... & Blagoev, B. (2021). Adipose MDM2 regulates systemic insulin sensitivity. *Scientific reports*, *11*(1), 1-17.

Hartz, A. J., Barboriak, P. N., Wong, A., Katayama, K. P., & Rimm, A. A. (1979). The association of obesity with infertility and related menstural abnormalities in women. International journal of obesity, 3(1), 57-73.

Haslam, D. (2010). Obesity and diabetes: the links and common approaches. Primary care diabetes, 4(2), 105-112.

Hehenkamp, W. J., Looman, C. W., Themmen, A. P., de Jong, F. H., Te Velde, E. R., & Broekmans, F. J. (2006). Anti-Mullerian hormone levels in the spontaneous menstrual cycle do not show substantial fluctuation. The Journal of Clinical Endocrinology & Metabolism, 91(10), 4057-4063.

Henquin, J. C. (2004). Pathways in beta-cell stimulus-secretion coupling as targets for therapeutic insulin secretagogues. Diabetes, 53(suppl_3), S48-S58.

Hillock-Watling, C., & Gotlieb, A. I. (2022). The pathobiology of perivascular adipose tissue (PVAT), the fourth layer of the blood vessel wall. Cardiovascular Pathology, 107459.

Hoogeveen, E. K. (2022). The Epidemiology of Diabetic Kidney Disease. Kidney and Dialysis, 2(3), 433-442.

Horton, E. S., Silberman, C., Davis, K. L., & Berria, R. (2010). Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. Diabetes care, 33(8), 1759-1765.

Howlader, M., Sultana, M. I., Akter, F., & Hossain, M. M. (2021). Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. Heliyon, 7(8), e07851.

Huang, X., Huang, X., Guo, H., Li, J., Zhou, C., Huang, Y., ... & Xie, C. (2022). Intermittent hypoxia-induced METTL3 downregulation facilitates MGLL-mediated lipolysis of adipocytes in OSAS. Cell death discovery, 8(1), 1-10.

Hussein, S. E. O., Osman, A. L., Higazi, H. M., Ali, S., & Alfeel, A. H. (2022). Influence of BMI on Serum Adiponectin, Resistine, and FBG among Overweight and Obese Females Diabetic Patient Type2. Open Access Macedonian Journal of Medical Sciences, 10(B), 1218-1221.

International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care, 2009, 32:1327-1334.

Ivanova, E. A., Myasoedova, V. A., Melnichenko, A. A., Grechko, A. V., & Orekhov, A. N. (2017). Small dense low-density lipoprotein as biomarker for atherosclerotic diseases. Oxidative medicine and cellular longevity, 2017.

Jain, A., Polotsky, A. J., Rochester, D., Berga, S. L., Loucks, T., Zeitlian, G., ... & Santoro, N. (2007). Pulsatile luteinizing hormone amplitude and progesterone metabolite excretion are reduced in obese women. The Journal of Clinical Endocrinology & Metabolism, 92(7), 2468-2473.

Jeyabalan, A., Hubel, C. A., & Davidge, S. T. (2022). Cardiometabolic Antecedents of Preeclampsia. In *Chesley's Hypertensive Disorders in Pregnancy* (pp. 245-264). Academic Press.

Jung, U. J., & Choi, M. S. (2014). Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. International journal of molecular sciences, 15(4), 6184-6223.

Jwad, S. M., & AL-Fatlawi, H. Y. (2022). Types of Diabetes and their Effect on the Immune System. Journal of Advances in Pharmacy Practices (e-ISSN: 2582-4465), 21-30.

Kadowaki, T. (2000). Insights into insulin resistance and type 2 diabetes from knockout mouse models. The Journal of clinical investigation, 106(4), 459-465.

Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. The Lancet, 383(9922), 1068-1083.

Kannel, W. B., Wilson, P. W., & Zhang, T. J. (1991). The epidemiology of impaired glucose tolerance and hypertension. American heart journal, 121(4), 1268-1273.

Karamanakos, G., Kokkinos, A., Dalamaga, M., & Liatis, S. (2022). Highlighting the Role of Obesity and Insulin Resistance in Type 1 Diabetes and Its Associated Cardiometabolic Complications. Current Obesity Reports, 1-23.

Karim, R. M., Naser, M. D., & AL-Fartosi, A. J. (2011). Lipid peroxidation and alkaline phosphotase levels in gastropod Lymnaea Radix cor (Annandale and Prashad, 1919) exposed to sublethal concentrations of endosulfan. Al-Kufa University Journal for Biology, 3(2).

Kawano, J., & Arora, R. (2009). The role of adiponectin in obesity, diabetes, and cardiovascular disease. Journal of the cardiometabolic syndrome, 4(1), 44-49.

Kawano, J., & Arora, R. (2009). The role of adiponectin in obesity, diabetes, and cardiovascular disease. Journal of the cardiometabolic syndrome, 4(1), 44-49.

Kazemi-Bonchenari, M., Khanaki, H., Jafari, A., Eghbali, M., Poorhamdollah, M., & Ghaffari, M. H. (2022). Milk feeding level and starter protein content: Effects on growth performance, blood metabolites, and urinary purine derivatives of Holstein dairy calves. Journal of Dairy Science

Keeter, W. C., Ma, S., Stahr, N., Moriarty, A. K., & Galkina, E. V. (2022, March). Atherosclerosis and multi-organ-associated pathologies. In Seminars in Immunopathology (pp. 1-12). Springer Berlin Heidelberg.

Kershaw, E. E., & Flier, J. S. (2004). Adipose tissue as an endocrine organ. The Journal of Clinical Endocrinology & Metabolism, 89(6), 2548-2556.

Khosla, S., Melton III, L. J., Atkinson, E. J., O'fallon, W. M., Klee, G. G., & Riggs, B. L. (1998). Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. The Journal of Clinical Endocrinology & Metabolism, 83(7), 2266-2274.+5+64

Klein, S., Gastaldelli, A., Yki-Järvinen, H., & Scherer, P. E. (2022). Why does obesity cause diabetes?. *Cell metabolism*, *34*(1), 11-20.

Koliaki, C., Liatis, S., & Kokkinos, A. (2019). Obesity and cardiovascular disease: revisiting an old relationship. Metabolism, 92, 98-107.

Kopelman, P. G. (2000). Obesity as a medical problem. Nature, 404(6778), 635-643.

Kopelman, P. G. (2000). Obesity as a medical problem. Nature, 404(6778), 635-643.

Koudele, A., Levy, G., Eyvazzadeh, A., Park, J., Klein, J., & BECKLEY, A. (2022). The predic Hartz, A. J., Barboriak, P. N., Wong, A., Katayama, K. P., & Rimm, A. A. (1979). The association of obesity with infertility and related menstural abnormalities in women. International journal of obesity, 3(1), 57-73.tive value of urinary Progesterone metabolite PdG testing in pregnancy outcomes.

Kubota, N., Yano, W., Kubota, T., Yamauchi, T., Itoh, S., Kumagai, H., ... & Kadowaki, T. (2007). Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell metabolism, 6(1), 55-68.

Kushner, Robert, Victor Lawrence, and Sudhesh Kumar. 2013. "The Genetic Basis of Obesity." Practical Manual of Clinical Obesity: 13–24.

Kyrou, I., Randeva, H. S., Tsigos, C., Kaltsas, G., & Weickert, M. O. (2018). Clinical problems caused by obesity. Endotext [Internet].

Lang, S., & Schnabl, B. (2020). Microbiota and fatty liver disease—the known, the unknown, and the future. *Cell host & microbe*, *28*(2), 233-244.

Lee, M. K., Cooney, O. D., Lin, X., Nadarajah, S., Dragoljevic, D., Huynh, K., ... & Loh, K. (2022). Defective AMPK regulation of cholesterol metabolism accelerates atherosclerosis by promoting HSPC mobilization and myelopoiesis. Molecular Metabolism, 61, 101514.

Lee, S. W., Hwang, I. S., Jung, G., Kang, H. J., & Chung, Y. H. (2022). Relationship between metabolic syndrome and follicle-stimulating hormone in postmenopausal women. Medicine, 101(18), e29216-e29216.

Lembo, E., Russo, M. F., Verrastro, O., Anello, D., Angelini, G., Iaconelli, A., ... & Capristo, E. (2022). Prevalence and predictors of non-alcoholic steatohepatitis in subjects with morbid obesity and with or without type 2 diabetes. Diabetes & Metabolism, 48(5), 101363.

Leonard, E. J., & Yoshimura, T. (1990). Human monocyte chemoattractant protein-1 (MCP-1). *Immunology today*, *11*, 97-101.

Leurs, P. B., Stolk, R. P., Hamulyak, K., Van Oerle, R., Grobbee, D. E., & Wolffenbuttel, B. H. (2002). Tissue factor pathway inhibitor and other endothelium-dependent hemostatic factors in elderly individuals with normal or impaired glucose tolerance and type 2 diabetes. Diabetes Care, 25(8), 1340-1345.

Levitsky, L. L., Drews, K. L., Haymond, M., Glubitosi-Klug, R. A., Katz, L. E. L., Mititelu, M., ... & TODAY Study Group. (2022). The obesity paradox: Retinopathy, obesity, and circulating risk markers in youth with type 2 diabetes in the TODAY Study. Journal of Diabetes and its Complications, 108259.

Bluhm, M. L., Hoehing, K. N., Nelson, R. K., & Zuhl, M. N. (2022). The impact of type-2 diabetes mellitus on cardiac rehabilitation outcomes: a meta-analysis. Archives of Physical Medicine and Rehabilitation.

Li, C. W., Yu, K., Shyh-Chang, N., Jiang, Z., Liu, T., Ma, S., ... & Liu, G. S. (2022). Pathogenesis of sarcopenia and the relationship with fat

mass: descriptive review. *Journal of Cachexia, Sarcopenia and Muscle*, *13*(2), 781-794.

Lihn, A. S., Bruun, J. M., He, G., Pedersen, S. B., Jensen, P. F., & Richelsen, B. (2004). Lower expression of adiponectin mRNA in visceral adipose tissue in lean and obese subjects. *Molecular and cellular endocrinology*, *219*(1-2), 9-15.

Lihn, A. S., Pedersen, S. B., & Richelsen, B. (2005). Adiponectin: action, regulation and association to insulin sensitivity. Obesity reviews, 6(1), 13-21.

Lim, P., & Bleich, D. (2022). Revisiting cardiovascular risk reduction in type 2 diabetes and dyslipidemia. International Journal of Cardiology Cardiovascular Risk and Prevention, 200141.

Lok, K. H., Wareham, N. J., Nair, R. S., How, C. W., & Chuah, L. H. (2022). Revisiting the concept of incretin and enteroendocrine L -cells as type 2 diabetes mellitus treatment. Pharmacological Research, 106237.

Lone, I. M., & Iraqi, F. A. (2022). Genetics of murine type 2 diabetes and comorbidities. Mammalian Genome, 1-16.

Lu, M., Tang, Q., Olefsky, J. M., Mellon, P. L., & Webster, N. J. (2008). Adiponectin activates adenosine monophosphate -activated protein kinase and decreases luteinizing hormone secretion in LβT2 gonadotropes. Molecular Endocrinology, 22(3), 760-771.

Lumeng, C. N., & Saltiel, A. R. (2011). Inflammatory links between obesity and metabolic disease. The Journal of clinical investigation, 121(6), 2111-2117.

Lyon, C. J., & Hsueh, W. A. (2003). Effect of plasminogen activator inhibitor–1 in diabetes mellitus and cardiovascular disease. The American journal of medicine, 115(8), 62-68.

Ma, L. J., Mao, S. L., Taylor, K. L., Kanjanabuch, T., Guan, Y., Zhang, Y., ... & Fogo, A. B. (2004). Prevention of obesity and insulin resistance in mice lacking plasminogen activator inhibitor 1. Diabetes, 53(2), 336-346.

Maahs, D. M., West, N. A., Lawrence, J. M., & Mayer-Davis, E. J. (2010). Epidemiology of type 1 diabetes. Endocrinology and Metabolism Clinics, 39(3), 481-497.

MALECHA-JĘDRASZEK, A. R. L. E. T. A., BURSKA, A., DONICA, H., MATUSZEK, B., & NOWAKOWSKI, A. (2012). Serum adiponectin concentration in patients with type 1 diabetes.

Manna, P., & Jain, S. K. (2015). Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: causes and therapeutic strategies. Metabolic syndrome and related disorders, 13(10), 423-444.

Martín-Timón, I., Sevillano-Collantes, C., Segura-Galindo, A., & del Cañizo-Gómez, F. J. (2014). Type 2 diabetes and cardiovascular disease: have all risk factors the same strength?. World journal of diabetes, 5(4), 444.

Maya, J., & Misra, M. (2022). The female athlete triad: review of current literature. Current Opinion in Endocrinology & Diabetes and Obesity, 29(1), 44-51.

Mehran, A. E., Templeman, N. M., Brigidi, G. S., Lim, G. E., Chu, K. Y., Hu, X., ... & Johnson, J. D. (2012). Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. Cell metabolism, 16(6), 723-737.

Meneghini, L. (2020). Insulin-Dependent Diabetes Mellitus (IDDM). Encyclopedia of Behavioral Medicine, 1202-1203.

Mitchell Jr, G. W., & Rogers, J. (1953). The influence of weight reduction on amenorrhea in obese women. New England Journal of Medicine, 249(21), 835-837.

Miura, Y., Yasuda, R., Toma, N., & Suzuki, H. (2022). Non-Fasting Hypertriglyceridemia Burden as a Residual Risk of the Progression of Carotid Artery Stenosis. *International Journal of Molecular Sciences*, *23*(16), 9197.

Morán-Costoya, A., Proenza, A. M., Gianotti, M., Lladó, I., & Valle, A. (2021). Sex Differences in Nonalcoholic Fatty Liver Disease: Estrogen

Influence on the Liver–Adipose Tissue Crosstalk. Antioxidants & Redox Signaling, 35(9), 753-774.

Moser, B., & Loetscher, P. (2001). Lymphocyte traffic control by chemokines. *Nature immunology*, *2*(2), 123-128.

Muoio, D. M., & Newgard, C. B. (2008). Molecular and metabolic mechanisms of insulin resistance and β-cell failure in type 2 diabetes. Nature reviews Molecular cell biology, 9(3), 193-205.

Natalucci, V., Virgili, E., Calcagnoli, F., Valli, G., Agostini, D., Zeppa, S. D., ... & Emili, R. (2021). Cancer Related Anemia: An Integrated Multitarget Approach and Lifestyle Interventions. Nutrients, 13(2), 482.

Nathan, D. M., Turgeon, H., & Regan, S. (2007). Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia, 50(11), 2239-2244.

National Institutes of Health. (2001). ATP III guidelines at-a-glance quick desk reference. NIH publication, 01-3305.

Nauck, M. (2016). Incretin therapies: highlighting common features and differences in the modes of action of glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Diabetes, Obesity and Metabolism, 18(3), 203-216.

Nawaz, S. S., & Siddiqui, K. (2022). Plasminogen activator inhibitor-1 mediate downregulation of adiponectin in type 2 diabetes patients with metabolic syndrome. Cytokine: X, 100064.

Neels, J. G., & Olefsky, J. M. (2006). Inflamed fat: what starts the fire?. The Journal of clinical investigation, 116(1), 33-35

Nibali, L., Gkranias, N., Mainas, G., & Di Pino, A. (2022). Periodontitis and implant complications in diabetes. Periodontology 2000.

Nyambuya, T. M., Dludla, P. V., & Nkambule, B. B. (2021). Diet-Induced Obesity Promotes the Upregulation of Fas Expression on T-cells. Biology, 10(3), 217.

O'Donnell, E., & O'Donnell, L. (2019). A Review of Type 1 Diabetes (T1D). Data Analytics in Medicine: Concepts, Methodologies, Tools, and Applications: Concepts, Methodologies, Tools, and Applications, 13.

Odell, W. D., Parlow, A. F., Swerdloff, R. S., Wabh, P. C., & Jacobs, H. S. (1981). Estimation of FSH test assay. Journal of clinical investigation, 47, 25-51.

Oku, A., Ueta, K., Arakawa, K., Ishihara, T., Nawano, M., Kuronuma, Y., ... & Endou, H. (1999). T-1095, an inhibitor of renal Na+-glucose cotransporters, may provide a novel approach to treating diabetes. Diabetes, 48(9), 1794-1800.

Onge, E. S., Miller, S. A., Motycka, C., & DeBerry, A. (2015). A review of the treatment of type 2 diabetes in children. The Journal of Pediatric Pharmacology and Therapeutics, 20(1), 4-16.

Ozougwu, J. C., Obimba, K. C., Belonwu, C. D., & Unakalamba, C. B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol, 4(4), 46-57.

Ozougwu, J. C., Obimba, K. C., Belonwu, C. D., & Unakalamba, C. B. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. J Physiol Pathophysiol, 4(4), 46-57.

Pamuk, F., & Kantarci, A. (2022). Inflammation as a link between periodontal disease and obesity. Periodontology 2000.

Panee, J. (2012). Monocyte Chemoattractant Protein 1 (MCP-1) in obesity and diabetes. Cytokine, 60(1), 1-12.

Park, K. G., Park, K. S., Kim, M. J., Kim, H. S., Suh, Y. S., Ahn, J. D., ... & Lee, I. K. (2004). Relationship between serum adiponectin and leptin concentrations and body fat distribution. Diabetes research and clinical practice, 63(2), 135-142.

Peng, Y. J., Shen, T. L., Chen, Y. S., Mersmann, H. J., Liu, B. H., & Ding, S. T. (2018). Adiponectin and adiponectin receptor 1

overexpression enhance inflammatory bowel disease. Journal of biomedical science, 25(1), 1-13.

Penney, A., Muhar, B. K., & Kotchoni, S. (2022). Biologics and Biosimilars Used for Diabetes. In Biologics and Biosimilars (pp. 269-280). CRC Press.

Periñán, M. T., Brolin, K., Bandres-Ciga, S., Blauwendraat, C., Klein, C., Gan-Or, Z., ... & Noyce, A. (2022). Effect modification between genes and environment, and Parkinson's disease risk. Annals of Neurology.

Broni, E. K., Ndumele, C. E., Echouffo-Tcheugui, J. B., Kalyani, R. R., Bennett, W. L., & Michos, E. D. (2022). The Diabetes-Cardiovascular Connection in Women: Understanding the Known Risks, Outcomes, and Implications for Care. Current diabetes reports, 1-15.

Murea, M., Ma, L., & Freedman, B. I. (2012). Genetic and environmental factors associated with type 2 diabetes and diabetic vascular complications. The review of diabetic studies: RDS, 9(1), 6.

Bonnefond, A., Froguel, P., & Vaxillaire, M. (2010). The emerging genetics of type 2 diabetes. Trends in molecular medicine, 16(9), 407-416.

Perk, J. et al. 2012. "Erratum: 'European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012)' the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constit." European Heart Journal 33(17): 2126.

Picu, A., Petcu, L., Ştefan, S., Mitu, M., Lixandru, D., Ionescu-Tîrgovişte, C., ... & Chifiriuc, M. C. (2017). Markers of oxidative stress and antioxidant defense in romanian patients with type 2 diabetes mellitus and obesity. Molecules, 22(5), 714.

Piemonti, L., Calori, G., Lattuada, G., Mercalli, A., Ragogna, F., Garancini, M. P., ... & Perseghin, G. (2009). Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular

disease mortality in middle-aged diabetic and nondiabetic individuals. Diabetes care, 32(11), 2105-2110.

Piemonti, L., Calori, G., Lattuada, G., Mercalli, A., Ragogna, F., Garancini, M. P., ... & Perseghin, G. (2009). Association between plasma monocyte chemoattractant protein-1 concentration and cardiovascular disease mortality in middle-aged diabetic and nondiabetic individuals. Diabetes care, 32(11), 2105-2110.

Pigeyre, M., & Meyre, D. (2018). Monogenic obesity. In Pediatric Obesity (pp. 135-152). Humana Press, Cham.

Pozo Garcia, L., Thomas, S. S., Rajesh, H., & Navaneethan, S. D. (2022). Progress in the management of patients with diabetes and chronic kidney disease. Current Opinion in Nephrology and Hypertension, 31(5), 456-463.

Prasad, M., Jayaraman, S., Eladl, M. A., El-Sherbiny, M., Abdelrahman, M. A. E., Veeraraghavan, V. P., ... & Rajagopal, P. (2022). A Comprehensive review on therapeutic perspectives of phytosterols in insulin resistance: A mechanistic approach. Molecules, 27(5), 1595.

Ramesh, G., MacLean, A. G., & Philipp, M. T. (2013). Cytokines and chemokines at the crossroads of neuroinflammation, neurodegeneration, and neuropathic pain. Mediators of inflammation, 2013.

Razali, N., Aziz, A. A., Lim, C. Y., & Junit, S. M. (2015). Investigation into the effects of antioxidant-rich extract of Tamarindus indica leaf on antioxidant enzyme activities, oxidative stress and gene expression profiles in HepG2 cells. PeerJ, 3, e1292.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reed, J., Bain, S., & Kanamarlapudi, V. (2021). A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes, metabolic syndrome and obesity: targets and therapy, 14, 3567.

Reese, J. M., Suman, V. J., Subramaniam, M., Wu, X., Negron, V., Gingery, A., ... & Hawse, J. R. (2014). ERβ1: characterization, prognosis, and evaluation of treatment strategies in ERα-positive and-negative breast cancer. BMC cancer, 14(1), 1-16.

Rega-Kaun, G., Kaun, C., & Wojta, J. (2013). More than a simple storage organ: adipose tissue as a source of adipokines involved in cardiovascular disease. Thrombosis and haemostasis, 110(10), 641-650.

Rhea, E. M., Banks, W. A., & Raber, J. (2022). Insulin Resistance in Peripheral Tissues and the Brain: A Tale of Two Sites. Biomedicines, 10(7), 1582.

Rogal, J., Zbinden, A., Schenke-Layland, K., & Loskill, P. (2019). Stem-cell based organ-on-a-chip models for diabetes research. Advanced Drug Delivery Reviews, 140, 101-128.

Rovin, B. H., & Song, H. (2006). Chemokine induction by the adipocyte-derived cytokine adiponectin. Clinical Immunology, 120(1), 99-105.

Ruderman, N., Chisholm, D., Pi-Sunyer, X., & Schneider, S. (1998). The metabolically obese, normal-weight individual revisited. Diabetes, 47(5), 699-713.

Saad, B., Kmail, A., & Haq, S. Z. (2022). Anti-Diabesity Middle Eastern Medicinal Plants and Their Action Mechanisms. Evidence-Based Complementary and Alternative Medicine, 2022.

Saad, B., Kmail, A., & Haq, S. Z. (2022). Anti-Diabesity Middle Eastern Medicinal Plants and Their Action Mechanisms. Evidence-Based Complementary and Alternative Medicine, 2022.

Sabanayagam, C., Sultana, R., Banu, R., Rim, T., Tham, Y. C., Mohan, S., ... & Jonas, J. B. (2021). Association between body mass index and diabetic retinopathy in Asians: the Asian Eye Epidemiology Consortium (AEEC) study. British Journal of Ophthalmology.

Sakers, A., De Siqueira, M. K., Seale, P., & Villanueva, C. J. (2022). Adipose-tissue plasticity in health and disease. Cell, 185(3), 419-446.

Salcedo, R., Ponce, M. L., Young, H. A., Wasserman, K., Ward, J. M., Kleinman, H. K., ... & Murphy, W. J. (2000). Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. Blood, The Journal of the American Society of Hematology, 96(1), 34-40.

Saponaro, C., Gaggini, M., Carli, F., & Gastaldelli, A. (2015). The subtle balance between lipolysis and lipogenesis: a critical point in metabolic homeostasis. Nutrients, 7(11), 9453-9474.

Sarmadi, M., Ahmadi-Soleimani, S. M., Fararouei, M., & Dianatinasab, M. (2021). COVID-19, body mass index and cholesterol: an ecological study using global data. *BMC Public Health*, *21*(1), 1-14.

Sasaki, N., Maeda, R., Ozono, R., Yoshimura, K., Nakano, Y., & Higashi, Y. (2022). Early-Phase Changes in Serum Free Fatty Acid Levels After Glucose Intake Are Associated With Type 2 Diabetes Incidenc e: The Hiroshima Study on Glucose Metabolism and Cardiovascular Diseases. Diabetes Care.

Schäfer, K., Fujisawa, K., Konstantinides, S., & Loskutoff, D. J. (2001). Disruption of the plasminogen activator inhibitor-1 gene reduces the adiposity and improves the metabolic profile of genetically obese and diabetic ob/ob mice. The FASEB Journal, 15(10), 1840-1842.

Schaible, U. E., & Kaufmann, S. H. E. (2007). Malnutrition and infection: complex mechanisms and global impacts. *PLoS medicine*, *4*(5), e115.

Ellulu, M. S., Patimah, I., Khaza'ai, H., Rahmat, A., & Abed, Y. (2017). Obesity and inflammation: the linking mechanism and the complications. Archives of medical science, 13(4), 851-863.

Misra, K., Dhillon, G. S., Brar, S. K., & Verma, M. (2014). Antioxidants. In Biotransformation of waste biomass into high value biochemicals (pp. 117-138). Springer, New York, NY.

Molnár, D., Decsi, T., & Koletzko, B. (2004). Reduced antioxidant status in obese children with multimetabolic syndrome. International Journal of Obesity, 28(10), 1197-1202.

Scheel, A. K., Espelage, L., & Chadt, A. (2022). Many Ways to Rome: Exercise, Cold Exposure and Diet—Do They All Affect BAT Activation and WAT Browning in the Same Manner?. International Journal of Molecular Sciences, 23(9), 4759.

Scherer, P. E. (2006). Adipose tissue: from lipid storage compartment to endocrine organ. Diabetes, 55(6), 1537-1545.

Scherer, P. E. (2016). The multifaceted roles of adipose tissue—therapeutic targets for diabetes and beyond: The 2015 Banting Lecture. Diabetes, 65(6), 1452-1461.

Schettler, G., & Nussel, E. (1975). Method for triglycerides. Aeb. Med. Soz. Med. Prav. Med, 10(25).

Sena, C. M., Pereira, A. M., & Seiça, R. (2013). Endothelial dysfunction—a major mediator of diabetic vascular disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1832(12), 2216-2231.

Shah, M. A., Haris, M., Faheem, H. I., Hamid, A., Yousaf, R., Rasul, A., ... & Althobaiti, N. A. (2022). Cross-Talk between Obesity and Diabetes: Introducing Polyphenols as an Effective Phytomedicine to Combat the Dual Sword Diabesity. Current Pharmaceutical Design.

Shahwan, M., Alhumaydhi, F., Ashraf, G. M., Hasan, P. M., & Shamsi, A. (2022). Role of polyphenols in combating Type 2 Diabetes and insulin resistance. International Journal of Biological Macromolecules.

Shahwan, M., Alhumaydhi, F., Ashraf, G. M., Hasan, P. M., & Shamsi, A. (2022). Role of polyphenols in combating Type 2 Diabetes a nd insulin resistance. International Journal of Biological Macromolecules.

Sharma, D., Arora, S., Banerjee, A., & Singh, J. (2021). Improved insulin sensitivity in obese-diabetic mice via chitosan Nanomicelles mediated silencing of pro-inflammatory Adipocytokines. Nanomedicine: Nanotechnology, Biology and Medicine, 33, 102357.

Shaw ND, Srouji SS, Histed SN, et al. Aging attenuates the pituitary response to gonadotropin-releasing hormone. J Clin Endocrinol Metab 2009;94:3259–64

Shaw, N. D., Histed, S. N., Srouji, S. S., Yang, J., Lee, H., & Hall, J. E. (2010). Estrogen negative feedback on gonadotropin secretion: evidence for a direct pituitary effect in women. The Journal of Clinical Endocrinology & Metabolism, 95(4), 1955-1961.

Singh, S., Anshita, D., & Ravichandiran, V. (2021). MCP-1: Function, regulation, and involvement in disease. *International immunopharmacology*, *101*, 107598.

SKONIECZNA-ŻYDECKA, K., PALMA, J., ŁONIEWSKI, I., & STACHOWSKA, E. (2021). I. SZYDŁOWSKA1, A. MARCINIAK1, A. BRODOWSKA1, B. LOJ2, S. CIEĆWIEŻ1. European Review for Medical and Pharmacological Sciences, 25, 3859-3867.

Snijder, M. B., Heine, R. J., Seidell, J. C., Bouter, L. M., Stehouwer, C. D., Nijpels, G., ... & Dekker, J. M. (2006). Associations of adiponectin levels with incident impaired glucose metabolism and type 2 diabetes in older men and women: the hoorn study. Diabetes care, 29(11), 2498 -2503.

Sobczak, Amélie IS, and Alan J. Stewart. "Coagulatory defects in type-1 and type-2 diabetes." International journal of molecular sciences 20.24 (2019): 6345.

Song, Y., Wang, E. S., Xing, L. L., Shi, S., Qu, F., Zhang, D., ... & Huang, H. F. (2016). Follicle-stimulating hormone induces

postmenopausal dyslipidemia through inhibiting hepatic cholesterol metabolism. The Journal of Clinical Endocrinology, 101(1), 254-263.

Stanimirovic, J., Radovanovic, J., Banjac, K., Obradovic, M., Essack, M., Zafirovic, S., ... & Isenovic, E. R. (2022). Role of C-Reactive Protein in Diabetic Inflammation. Mediators of Inflammation, 2022.

Stefanska, A., Ponikowska, I., Cwiklinska-Jurkowska, M., & Sypniewska, G. (2014). Association of FSH with metabolic syndrome in postmenopausal women: a comparison with CRP, adiponectin and leptin. Biomarkers in medicine, 8(7), 921-930.

Stefanska, A., Sypniewska, G., Ponikowska, I., & Cwiklinska-Jurkowska, M. (2012). Association of follicle-stimulating hormone and sex hormone binding globulin with the metabolic syndrome in postmenopausal women. Clinical biochemistry, 45(9), 703-706.

Suleiman, M., Marselli, L., Cnop, M., Eizirik, D. L., De Luca, C., Femia, F. R., ... & Marchetti, P. (2022). The Role of Beta Cell Recovery in Type 2 Diabetes Remission. International journal of molecular sciences, 23(13), 7435.

Takahashi, M., Yamamuro, D., Wakabayashi, T., Takei, A., Takei, S., Nagashima, S., ... & Ishibashi, S. (2022). Loss of myeloid lipoprotein lipase exacerbates adipose tissue fibrosis with collagen VI deposition and hyperlipidemia in leptin-deficient obese mice. Journal of Biological Chemistry, 102322.

Taylor, A. E., McCourt, B., Martin, K. A., Anderson, E. J., Adams, J. M., Schoenfeld, D., & Hall, J. E. (1997). Determinants of abnormal gonadotropin secretion in clinically defined women with polycystic ovary syndrome. The journal of clinical endocrinology & metabolism, 82(7), 2248-2256.

Thompson, K. A., & Kanamarlapudi, V. (2013). Type 2 diabetes mellitus and glucagon like peptide-1 receptor signalling. Clinical & Experimental Pharmacology, 3(04).

Thompson, K. A., & Kanamarlapudi, V. (2013). Type 2 diabetes mellitus and glucagon like peptide-1 receptor signalling. Clinical & Experimental Pharmacology, 3(04).

Thorne, S., Paterson, B., & Russell, C. (2003). The structure of everyday self-care decision making in chronic illness. Qualitative health research, 13(10), 1337-1352.

Toth, P. P., Barter, P. J., Rosenson, R. S., Boden, W. E., Chapman, M. J., Cuchel, M., ... & Rader, D. J. (2013). High-density lipoproteins: a consensus statement from the National Lipid Association. Journal of clinical lipidology, 7(5), 484-525.

Tricò, D., McCollum, S., Samuels, S., Santoro, N., Galderisi, A., Groop, L., ... & Shabanova, V. (2022). Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach. Diabetes care, 45(8), 1841-1851.

Tricò, D., McCollum, S., Samuels, S., Santoro, N., Galderisi, A., Groop, L., ... & Shabanova, V. (2022). Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach. Diabetes care, 45(8), 1841-1851.

Tricò, D., McCollum, S., Samuels, S., Santoro, N., Galderisi, A., Groop, L., ... & Shabanova, V. (2022). Mechanistic Insights Into the Heterogeneity of Glucose Response Classes in Youths With Obesity: A Latent Class Trajectory Approach. Diabetes care, 45(8), 1841-1851.

Tripathi, B. K., & Srivastava, A. K. (2006). Diabetes mellitus: complications and therapeutics. Med Sci Monit, 12(7), 130-47.

Trujillo-Viera, J., El-Merahbi, R., Schmidt, V., Karwen, T., Loza-Valdes, A., Strohmeyer, A., ... & Sumara, G. (2021). Protein Kinase D2 drives chylomicron-mediated lipid transport in the intestine and promotes obesity. EMBO molecular medicine, 13(5), e13548.

Tsatsanis, C., Zacharioudaki, V., Androulidaki, A., Dermitzaki, E., Charalampopoulos, I., Minas, V., ... & Margioris, A. N. (2005). Adiponectin induces TNF-α and IL-6 in macrophages and promotes tolerance to itself and other pro-inflammatory stimuli. Biochemical and biophysical research communications, 335(4), 1254-1263.

Van Arensbergen, J., García-Hurtado, J., Moran, I., Maestro, M. A., Xu, X., Van de Casteele, M., ... & Ferrer, J. (2010). Derepression of Polycomb targets during pancreatic organogenesis allows insulin-

producing beta-cells to adopt a neural gene activity program. Genome research, 20(6), 722-732.

van Duinkerken, E., & Ryan, C. M. (2020). Diabetes mellitus in the young and the old: Effects on cognitive functioning across the life span. Neurobiology of disease, 134, 104608.

Van Greevenbroek, M. M., Schalkwijk, C. G., & Stehouwer, C. D. (2013). Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. Neth J Med, 71(4), 174-87.

Visser, J. A., de Jong, F. H., Laven, J. S., & Themmen, A. P. (2006). Anti-Mullerian hormone: a new marker for ovarian function. Reproduction, 131(1), 1-9.

WALDSTREICHER, J., SANTORO, N. F., HALL, J. E., FILICORI, M., & CROWLEY JR, W. F. (1988). Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian disease: indirect evidence for partial gonadotroph desensitization. The Journal of Clinical Endocrinology & Metabolism, 66(1), 165-172.

Walz, A., Peveri, P., Aschauer, H., & Baggiolini, M. (1987). Purification and amino acid sequencing of NAF, a novel neutrophil-activating factor produced by monocytes. Biochemical and biophysical research communications, 149(2), 755-761.

Wang, N., Kuang, L., Han, B., Li, Q., Chen, Y., Zhu, C., ... & Lu, Y. (2016). Follicle-stimulating hormone associates with prediabetes and diabetes in postmenopausal women. Acta diabetologica, 53(2), 227-236.

Wang, X., Chen, C., Xie, C., Huang, W., Young, R. L., Jones, K. L., ... & Wu, T. (2022). Serum bile acid response to oral glucose is attenuated in patients with early type 2 diabetes and correlates with 2-hour plasma glucose in individuals without diabetes. Diabetes, Obesity and Metabolism, 24(6), 1132-1142.

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., & Ferrante, A. W. (2003). Obesity is associated with macrophage accumulation in adipose tissue. The Journal of clinical investigation, 112(12), 1796-1808.

Weng, J., Ji, L., Jia, W., Lu, J., Zhou, Z., Zou, D., ... & Chinese Diabetes Society. (2016). Standards of care for type 2 diabetes in China. Diabetes/metabolism research and reviews, 32(5), 442.

WHO Expert Consultation Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–163.

Wild, S. H., & Byrne, C. D. (2013). Commentary: Sub-types of diabetes—what's new and what's not. International journal of epidemiology, 42(6), 1600-1602.

Wilding, J. (2014). The importance of weight management in type 2 diabetes mellitus. International journal of clinical practice, 68(6), 682-691.

Xue, D., Zheng, Y., Wen, J., Han, J., Tuo, H., Liu, Y., & Peng, Y. (2021). Role of chemokines in hepatocellular carcinoma. *Oncology Reports*, *45*(3), 809-823.

Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007; 13: 332 –339.

Yamauchi, T., & Kadowaki, T. (2008). Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. International journal of obesity, 32(7), S13-S18

Yamauchi, T., Iwabu, M., Okada-Iwabu, M., & Kadowaki, T. (2014). Adiponectin receptors: a review of their structure, function and how they work. Best practice & research Clinical endocrinology & metabolism, 28(1), 15-23.

Yazdanpanah, S., Rabiee, M., Tahriri, M., Abdolrahim, M., & Tayebi, L. (2015). Glycated hemoglobin-detection methods based on electrochemical biosensors. TrAC Trends in Analytical Chemistry, 72, 53-67.

Ye, J. (2013). Mechanisms of insulin resistance in obesity. Frontiers of medicine, 7(1), 14-24.

Yoshimura, T., Matsushima, K., Oppenheim, J. J., & Leonard, E. J. (1987). Neutrophil chemotactic factor produced by lipopolysaccharide (LPS)-stimulated human blood mononuclear leukocytes: partial characterization and separation from interleukin 1 (IL 1). The Journal of Immunology, 139(3), 788-793.

Zhang, S., Huang, Y. P., Li, J., Wang, W. H., Zhang, M. Y., Wang, X. C., ... & Li, C. J. (2022). The Visceral-Fat-Area-to-Hip-Circumference Ratio as a Predictor for Insulin Resistance in a Chinese Population with Type 2 Diabetes. Obesity Facts, 1-8.

Zhang, Z., Du, J., Shi, H., Wang, S., Yan, Y., Xu, Q., ... & Li, F. (2022). Adiponectin suppresses tumor growth of nasopharyngeal carcinoma through activating AMPK signaling pathway. Journal C. M. Diaz-Melean, V. K. Somers, and J. P. Rodriguez-Escudero, "Mechanisms of adverse cardiometabolic consequences of obesity," Current Atherosclerosis Reports, vol. 15, no. 11, p. 364, 2013.

Zhou, Y., & Xu, B. (2022). New insights into anti-diabetes effects and molecular mechanisms of dietary saponins. Critical Reviews in Food Science and Nutrition, 1-26.

Zhu, B., Li, Y., Mei, W., He, M., Ding, Y., Meng, B., ... & Xiang, G. (2019). Alogliptin improves endothelial function by promoting autophagy in perivascular adipose tissue of obese mice through a GLP-1-dependent mechanism. Vascular pharmacology, 115, 55-63.

Classification and diagnosis of diabetes. Diabetes Care. American Diabetes Association. 2017;39(1):S13-S22.

Qadir I. Advancement In Therapeutic Efforts And Tools For Prevention And Treatment Of Insulin Dependent Diabetes Mellitis. Pakistan Journal of Pharmaceutical Research. 2018;3(2):66-76.

Association AD. 14. Diabetes Care in the Hospital: Standards of Medical Care in Diabetes—2018. Diabetes Care. 2018;41(Supplement 1):S144-S51.

Aleem S, Iqbal R, Shar T, Noreen S, Rafiq N, Javed I, et al. Complications of Diabetes: An Insight into Genetic Polymorphism and Role of Insulin. Recent patents on inflammation & allergy drug discovery. 2018;12(1):78-86.

Jin W, Patti M-E. Genetic determinants and molecular pathways in the pathogenesis of Type 2 diabetes. Clinical Science. 2009;116(2):99-111..

.Association AD. Diagnosis and classification of diabetes mellitus Diabetes care. 2014;37(Supplement 1):S81-S90.

Nathan DM, McGee P, Steffes MW, Lachin JM, group DEr. Relationship of glycated albumin to blood glucose and glycated hemoglobin (HbA1C) values and to retinopathy, nephropathy and cardiovascular outcomes in the DCCT/EDIC study. Diabetes. 2014: 63(1): 282-290

Hayyan M, Hashim MA, AlNashef IM. Superoxide ion: generation and chemical implications. Chemical reviews. 2016;116(5):3029-3085

Hadwan, M. H. (2008). The activities of Catalase in the Spermatozoa and Seminal Plasma of Patients with Asethenospermia; and their Relationship with Oxidants and Antioxidants. Iraqi Natl J Chem, 31, 514-521.

Weykamp, C. (2013). HbA1c: a review of analytical and clinical aspects. *Annals of laboratory medicine*, *33*(6), 393.

Kalia, V., & Pundir, C. S. (2004). Determination of serum triglycerides using lipase, glycerol kinase, glycerol-3-phosphate oxidase and peroxidase co-immobilized onto alkylamine glass beads.