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"The assessment of Insulin Like Growth Factor-1 changes in diabetic patients"

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

"وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ"

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تقييم التغيرات في عامل النمو الشبيه بالأنسولين -1 لدى مرضى السكري

الخلاصة

يحسن التحكم في نسبة السكر في الدم ويقلل IGF-I على الرغم من أن مرض السكري هو حالة غير متجانسة، فقد ثبت أن يوجد الآن دليل مقنع على أن هذا يرتبط بانخفاض إفراز هرمون النمو .NIDDMو IDDM متطلبات الأنسولين في كل من مما يؤدي إلى تحسن في حساسية الأنسولين والتحكم في نسبة السكر في الدم. قد تكون الآلية ببساطة هي تقليل إفراز هرمون IGF-I النمو، ولكن من المحتمل أيضًا حدوث تأثيرات ما قبل وبعد المستقبل على حساسية الأنسولين. من المحتمل أن يكون لـ غير واضحة. الهدف من الدراسة هو دراسة مستويات IGF-I ، تظل آلية عملDM تأثير مباشر على استقلاب الجلوكوز. في ومقارنتها مع الأشخاص الخاضعين للمراقبة DM لدى هؤلاء المرضى من النوع 1 والنوع 2 IGF-1 و C البيتيد

الطُرق

في إجمالي IGF-1 مع مستوى C قمنا بتقييم العلاقة المحتملة بين مرض السكري وحالة وظيفة الخلية بيتا كمستويات البيتيد ن = 30). 32) والمجموعة الضابطة (ن) 2 DM ن = 30)، نوع) 1 DM 112 شخصًا مقسمين إلى ثلاث مجموعات، نوع IGF-1البيتيد و-C = 50). تمت متابعة المشاركين من خلال استبيان تم إجراؤه بواسطة فاحصين مدربين تدريباً جيداً. تم تقييم في كلا المجموعتين

النتائج

في كلا المجموعتين المصابتين بالسكري مقارنة بالمجموعة الضابطة، مع وجود IGF-1 كانت هناك مستويات عالية من ومستويات السكر في الدم عند التشخيص بين المجموعتين المصابتين بالسكري C فروق ذات دلالة إحصائية في البيتيد وبالمقارنة مع مجموعة السيطرة أيضًا

الخاتمة

C بشكل متناسب مع مستوى الأنسولين لدى مرضى السكري مع وجود علاقة إيجابية مع مستويات البيتيد IGF-1 قد يرتبط مع الحفاظ على وظيفة خلايا بيتا المتبقية على المدى الطويل

Abstract

Although diabetes is a heterogeneous condition, IGF-I has been shown to improve glycaemic control and reduce insulin requirements in both IDDM and NIDDM. There is now convincing evidence that this is associated with a reduction in GH secretion resulting in an improvement in insulin sensitivity and glycaemic control. The mechanism may simply be reduced GH-secretion, but pre- and post-receptor effects on insulin sensitivity are also likely. IGF-I is likely to be have a direct effect on glucose metabolism. In DM, the mechanism of action of IGF-I remains unclear. The aim of study is to investigate the levels of C-peptide and IGF-1 levels in these patients of type 1 and type 2 DM and compare them with control subjects.

Methods

We assessed the possible relationship between diabetes and β-cell function status as C-peptide levels with the level of IGF-1 in total 112 subjects divided into three groups, the DM type 1(n=30), DM type 2 (n=32) and the control group (n=50). Participants were followed up a questionnaire that was done by well-trained examiners. C-peptide and IGF-1 were assessed in both groups.

Results

There were high IGF-1 levels in both diabetic groups compared with the control group, with statistically significant differences in C-peptide and blood sugar levels at diagnosis between the two diabetic groups and in comparison to the control group also.

Conclusion

IGF-1 may be proportionally associated with the level of insulin in diabetic patients with a positive relation to C-peptide levels with long term preservation of residual β-cell function.

Keywords: Diabetes mellitus type 1, Diabetes mellitus type 2, C-peptide, IGF-1, residual beta cell function

1. DIABETES MELLITUS

1.1 OVERVIEW

The pancreas produces the peptide hormones insulin, glucagon, and somatostatin. The peptide hormones are secreted from cells in the islets of Langerhans ((3-cells produce insulin, a cells produce glucagon, and 5 cells produce somatostatin). These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result [1].

The incidence of diabetes is growing rapidly in the United States and worldwide. An estimated 30.3 million people in the United States and 422 million people worldwide are afflicted with diabetes. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin. The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes due to other causes such as genetic defects or medications [2].

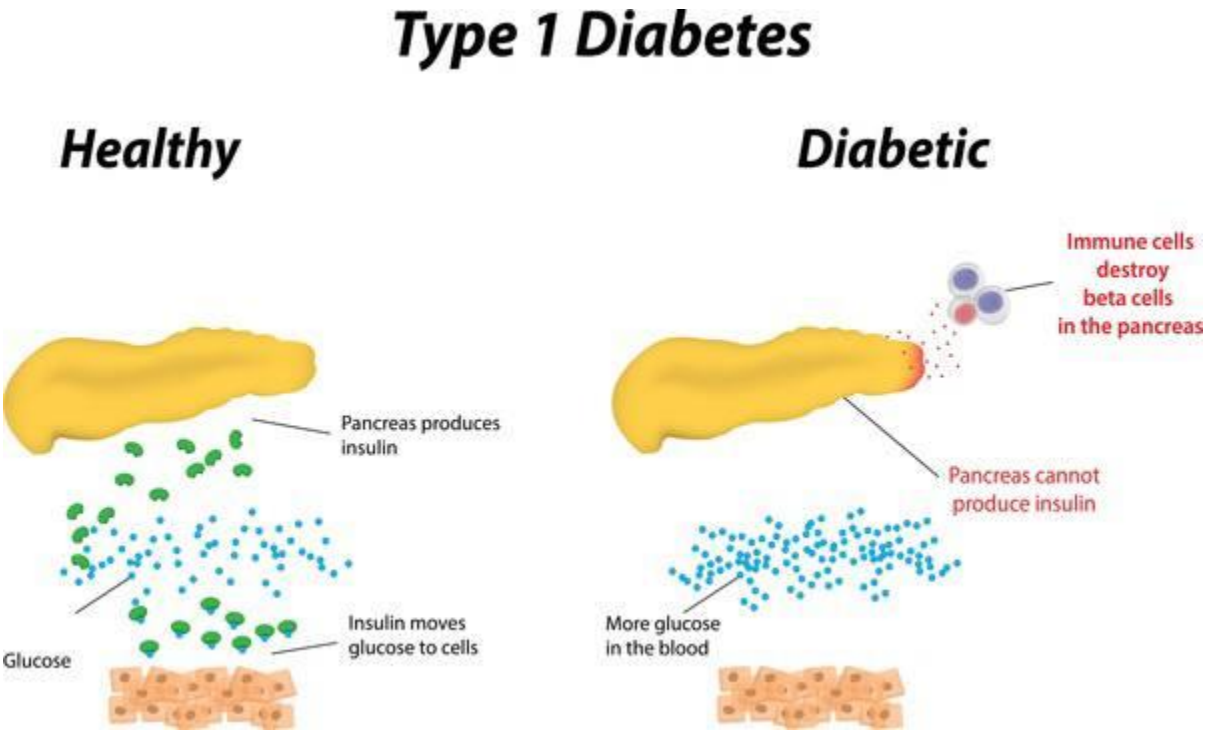
1.2. Type 1 diabetes

Type 1 diabetes most commonly afflicts children, adolescents, or young adults, but some latent forms occur later in life. The disease is characterized by an absolute deficiency of insulin due to destruction of p cells. Without functional f3 cells, the pancreas fails to respond to glucose, and a person with type 1 diabetes shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss) [3].

Causes: Loss of cell function in type 1 diabetes results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins. In patients without diabetes, constant cell secretion maintains low basal levels of circulating insulin. This suppresses lipolysis, proteolysis, and glycogenolysis. A burst of insulin secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in circulating glucose and amino acids.

	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%–10%	90%–95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

This lasts for up to 15 minutes, followed by the postprandial secretion of insulin. However, without functional cells, those with type 1 diabetes can neither maintain basal secretion of insulin nor respond to variations in circulating glucose [2].

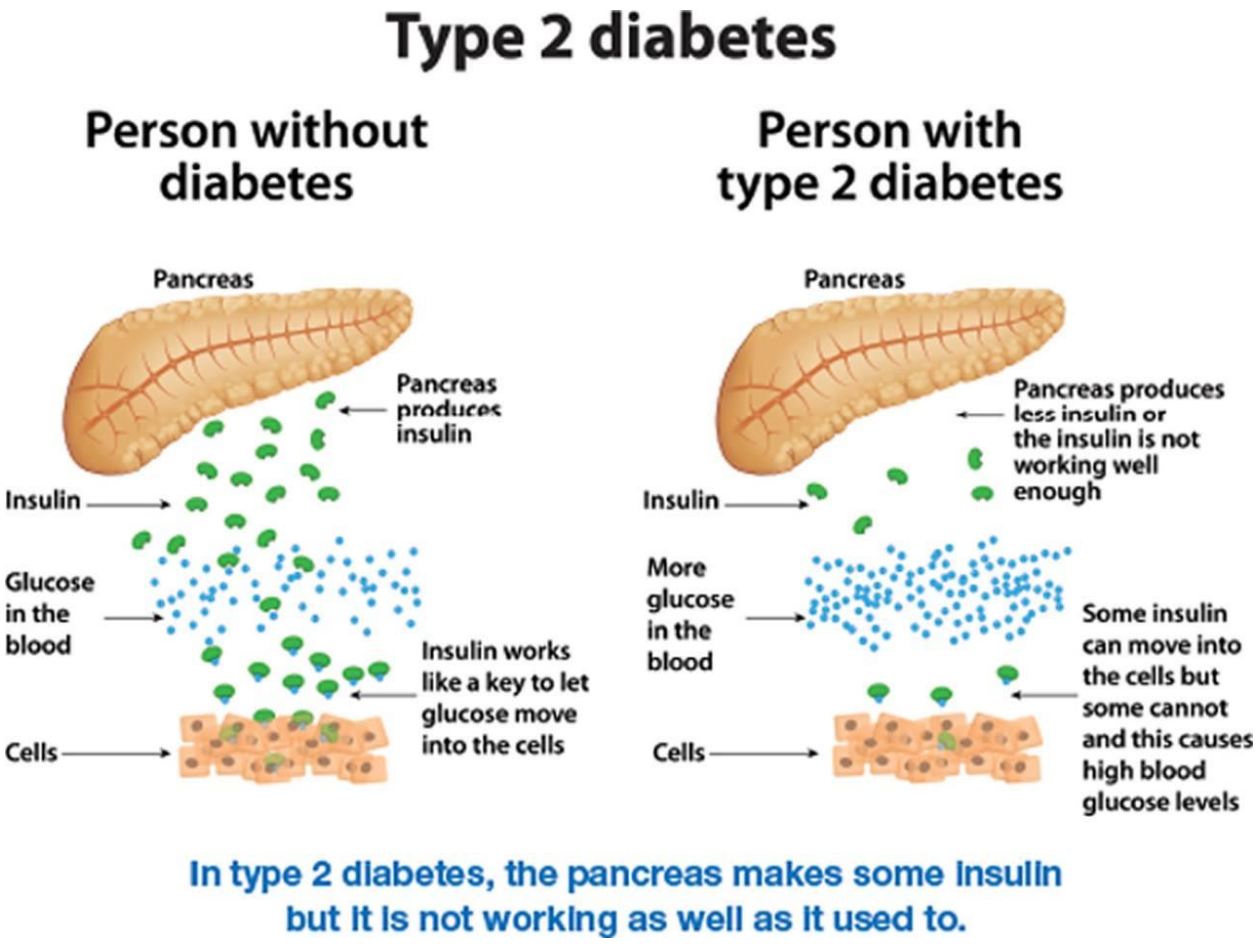


Treatment: A person with type 1 diabetes must rely on exogenous insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c). [Note: HbA1c is a marker of overall glucose control and is used to monitor diabetes in clinical practice. The rate of formation of HbA1c is proportional to the average blood glucose concentration over the previous 3 months. A higher average glucose results in a higher HbA1c. The goal of insulin therapy in type 1 diabetes is to maintain blood glucose as close to normal as possible and to avoid wide fluctuations in glucose. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin [4].

1.3. Type 2 diabetes:

Type 2 diabetes accounts for greater than 90% of cases. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes. The metabolic alterations are generally milder than those observed with type 1 diabetes (for example, patients with type 2 diabetes typically are not ketotic), but the long-term clinical consequences are similar [5].

Causes: Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin.



Treatment: The goal in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes. However, most patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, cell function declines, and insulin therapy is often needed to achieve satisfactory glucose levels.

Oral agents are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet. Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycemia [6].

A. Sulfonylureas

These agents are classified as insulin secretogenous, because they promote insulin release from the cells of the pancreas. The sulfonylureas most used in clinical practice are the second-generation drugs [7].

B. Glinides

This class of agents are also considered insulin secretogenous [7].

C. Biguanides

Metformin the only biguanide, is classified as an insulin sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance. Unlike sulfonylureas, metformin does not promote insulin secretion. Therefore, the risk of hypoglycemia is far less than that with sulfonylureas. Metformin is also useful

in the treatment of polycystic ovary syndrome, as it reduces insulin resistance seen in this disorder [7].

D. Thiazolidinediones

The thiazolidinediones (TZDs) are also insulin sensitizers. The two agents in this class are pioglitazone and rosiglitazone Although insulin is required for their action, the TZDs do not promote its release from the cells, so hyperinsulinemia is not a risk.

E. a-Glucosidase inhibitors

Acarbose and are oral agents used for the treatment of type 2 diabetes.

F. Dipeptidyl peptidase-4 inhibitors

are oral dipeptidyl peptidase-4 {DPP-4) inhibitors used for the treatment of type 2 diabetes.

G. Sodium-glucose cotransporter 2 inhibitors

are oral agents for the treatment of type 2 diabetes. Empagliflozin is also indicated to reduce the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease [8].

1.4. Diagnosing Type 2 Diabetes.

1. Fasting Blood Glucose (FBG): Before taking the blood test, the person should have taken no food for at least 8 hours. The easiest way to do this is to arrange an appointment for the patient to have the blood test first thing in the morning. They should fast overnight and must not have anything to eat until after the test. Fasting plasma glucose is escribed as a fasting blood glucose level of ≥ 126 mg/dl [9].

2. Random Blood Glucose- Sugar level or blood glucose measured at any time of day without regard to time since the last meal. It does not take into account what the patient has been eating or drinking. It is therefore less sensitive than the other tests. However, it is the easiest to perform. Where a random plasma glucose level more than and equal to 100 mg/dl and less than 200 mg/dl is detected, a FPG should be measured, or an OGTT performed, or an HbA1c measured. However, as explained earlier, for the purpose of SCREENING, random blood sugar over 140 mg/dl is taken as requiring further follow-up [9].

3. Two- hour venous plasma glucose after ingestion of 75g oral glucose load (Oral Glucose Tolerance Test- OGTT). The Oral Glucose Tolerance Test (OGTT) is a method which is used to diagnose Type 2 diabetes by measuring how well the body's cells are able to absorb a fixed amount of sugar or glucose.

4. HbA1c (Glycosylated, or Glycated haemoglobin): It is a form of haemoglobin in the RBCs. The HbA1c level is proportional to average blood glucose over the previous two to three months. It is an excellent indicator of how well the patient has managed his/her diabetes over the last four weeks to three months. It is recommended for monitoring blood sugar control in diabetic patients. However, the test is more costly than blood glucose measurement. WHO recommends an HbA1c goal of less than 6.5 % for people with diabetes [10].

2. Inslin like growth factor

The insulin-like growth factor (IGF) system is involved in the regulation of mammalian cell growth and differentiation, proliferation, and survival [11]. The system affects any of the other systems in our body. IGF-1 is a small protein consisting of 70 amino acids, with a molecular weight of 7.65 kilo Dalton, and the

gene is located at chromosome 12q23 [11]. It is mainly produced by liver cells, but also by many other cells in our body [12].

The IGF system consists of:

1- 2 cell-surface receptors (IGF-1R and IGF-2R)
2- 2 ligands (IGF-1 and IGF-2)
3- 6 high-affinity IGF-binding proteins (IGFBP-1 toIGFBP-6) [13,14]
4- Several associated IGFBP degrading protease enzymes.

The entire system is strongly controlled by a feedback loop involving growth hormones (GH) secreted by the pituitary, and GH production and secretion controlled by growth hormone-releasing hormone (GHRH) in the hypothalamus

IGF-1 and IGFBP-3 are GH-dependent [15], while IGFBP-1 is insulin-regulated. IGFBP-1 production from the liver is significantly elevated during insulinopenia, and serum levels of bioactive IGF-1 are increased by insulin [16,17]. The production of IGFBP-3, -4, and -5 is stimulated by GH. IGFBP-3 is formed by the liver sinusoidal cells at the junction of the intravascular space. In circulation, IGF-1 is mainly bound to IGFBP-3, and this binary complex then binds to a large protein called the acid-labile subunit (ALS) to form a ternary complex [18, 19].

Insulin and IGF-1 are two related peptides with similar structure. They exercise their effects by interacting with their corresponding receptors, namely the insulin receptor and IGF-1R. The receptor-ligand interactions induce intracellular signaling cascades resulting in metabolic or mitogenic effects [20, 21] and are involved in regulation of metabolism. In contrast, IGF-1 overproduction in some pancreatic and non-pancreatic cancers has been linked to severe hypoglycemia [21].

Insulin encourages the constitutive secretion of IGF-1 from the liver. In turn, IGF-1 overruns insulin secretion even in normoglycemic situations [22]. Furthermore, a

previous study showed that IGF-1 causes insulin activity and peripheral glucose utilizations to increase, hepatic glucose production to decrease, and lipid profiles in diabetes patients to improve [23].

IGFBP-1 is regulated mainly by insulin. It interacts with IGF-1 and IGF-2, and is used as a shuttle for IGFs to target tissues and regulate the action of free IGF-1. IGFPB-1 is regarded as the primary regulator of IGF-1 bioactivity and has an important part in the progression of diabetes and diabetes-related complications [24]. Lewitt et al. reported that the IGF system has an imperative pathophysiological role across a range of metabolic abnormalities, including obesity, insulin resistance (IR), and diabetes [25].

The exact mechanisms by which type 1 diabetes (T1D) and poor glycemic control relate to the GH-axis and its interaction with IGF-1 and IGFBP-3 remain to be determined. Nambam and Schatz have shown that GH insensitivity in combination with low concentrations of IGF-1 is frequently observed in T1D patients [26]. However, controversies have been described in diabetes complications such as diabetic retinopathy (DR) [27]. According to Bazzaz et al., growth factors are associated with the development of DR, diabetic nephropathy (DN), and diabetic neuropathy (DNP). However, this article showed that growth factors, including vascular endothelial growth factor (VEGF), IGF-1, and tumor necrosis growth factor, may have a protective role in the progression and development of diabetes complications [28].

The pathogenesis of DR is a complex process involving ischemia and hyperglycemia; growth factors may result in neovascularization and loss of vision. There is controversy about the serum IGF-1 level that correlates with the progression of retinal neovascularization in clinical diabetes and increased or decreased concentrations of IGF-1 in the vitreous or serum levels of patients with DR [29].

Neam u et al. showed that decreased concentrations of IGF-1 were positively correlated with diabetes and diabetes-related complications [30].

Evidence has suggested that patients with T1D may have aberrations of the GH/IGF/IGFBP axis, including GH hypersecretion, decreased concentrations of circulating IGF-1 and IGFBP-3, and elevated levels of IGFBP-1 [12]. These abnormalities may exacerbate hyperglycemia in patients with T1D and play a role in the pathogenesis of diabetes-related complications [31]. Also, IGF-1 deficit has been reported to be significantly associated with the risk of developing impaired glucose tolerance, IR, and type 2 diabetes mellitus (T2D) [22]. The study also suggested that IGF-1 deficit may be a factor in the pathogenesis of schizophrenia [32]. Knott in 1998 presented a clear association between high levels of IGF-1 and the progression of DR [23].

2.2. The physiology of the IGF system

The IGF system is encompassed of IGFs, IGF-1 and IGF-2 receptors, IGFBPs and IGFBP-specific proteases [9]. Roith et al. stated that IGF decreases the chance of developing diabetes, cancer, and malnutrition [24, 25]. The IGF regulatory systems in different organs are tissue-specific, including liver, kidney, heart, and other tissues, but all share similar components [26-28].

IGF-1 and IGFBP-1 are regulated by pituitary GH and IGFBP-3. IGF-1 and IGFBP-3 form complexes that bind to the acid-labile subunit (ALS) and prevent the premature degradation of IGF-1 by circulating IGF-1 proteases. Its release into the extravascular space extends the half-life of IGF-1 and initiates the transport into specific target tissues [16]. Aguirre et al. reported that IGF-2 has similar physiological properties to IGF-1, and its actions have remained poorly

characterized, but the appropriate roles in fetal growth and development and cerebral protection have been documented well [29].

2.3. Physiology of insulin and IGFs

Insulin is secreted by β-cells in the pancreas. It has both endocrine and exocrine function. Insulin consists of two peptide chains, “A” and “B”. The other “C”-peptide is formed and cleaved off when pro-insulin transforms to active insulin. Insulin increases glucose uptake in muscle and fat by stimulating the translocation of glucose transporter 4 from the cytoplasm to the cell surface, but inhibits glucose production in the liver. It also stimulates lipogenesis, glycogen, protein synthesis, and cell growth and differentiation. The functional defect and deficiency of insulin both cause diabetes to develop accompanied by elevated fasting and postprandial glucose levels and elevated free fatty acid levels [10].

The GH-IGF axis requires the hypothalamic pituitary axis for production of GH, its receptor for IGF production, IGFBP for transport of IGF, and IGF receptor for IGF action [30]. Laron et al. suggested that IGF-1 acts as an endocrine hormone that is secreted by hepatocytes and transported to other tissues [31]. They also found that it is secreted by other tissues as well including cartilaginous cells, acts locally as a paracrine hormone, and may act in an autocrine manner in oncogene [31]. IGF and insulin are proteins with high amino acid sequence similarity. They have structural similarity, but control different aspects of growth, development, and metabolism. IGF-1 and insulin fully activate IGF-1R and insulin receptor, but they can also interact with each other and activate the other receptor with low affinity [17, 26, 32, 33].

2.4. Interactions of insulin receptor and IGFs

Both insulin and IGF-1 have their own receptors, namely insulin receptor and IGF-1R, which originate from the same family of tyrosine kinase receptors [10]. Lewitt et al. stated that IGFs interact with insulin receptor A and B isoforms, IGF-1R, and hybrid receptors, including insulin receptor A-IGF-1R and insulin receptor B-IGF-1R. This interaction is used to mediate signals in various tissues in order to harmonize protein, carbohydrate, and fat metabolism. Interestingly, liver cells and mature adipose tissue cells have ample insulin receptor B, and insulin has a 2-fold higher affinity for insulin receptor B than IGF-1 [15].

The IGF-1 receptor has been found in various body systems, including brain, testes, liver, and bones. This suggests an important paracrine and endocrine role of IGF. Insulin binds to the IGF-1 receptor with lower potency compared to IGFs, and IGF binds to the insulin receptor to activate the reduction in blood glucose levels in the body [36]. IGF-2R binds to IGF-2, almost exclusively, and plays a minor role in the growth-promoting effect of IGF [30, 31].

A previous study reported that nutrition and GH stimulate the synthesis of IGF-1 in liver and other tissues. The study revealed that there are gender differences in the hepatic sensitivity to GH, and that women require more GH to synthesize IGF-1 in liver and other tissues [37]. IGFs that reach the pituitary hinder GH synthesis in a feedback loop. GH has an imperative metabolic role independent of IGF-1 effects, stimulation of lipolysis, and inhibitory effects on insulin signaling in fat and muscle cells [38]. Thus, IGF feedback inhibition of GH by dropping the direct metabolic effects may improve insulin sensitivity. Dynkevich et al. concluded that IGFs directly control protein, carbohydrate, and fat metabolism, and IGF-1 also augments insulin sensitivity independent of its consequence on GH [39].

2.5. Insulin-like growth factor-binding proteins (IGFBPs)

The IGFBP family is a critical component of the IGF system; it controls the biological actions of the IGFs and may also be capable of IGF-independent actions [33]. Back et al. have reported IGFBPs to be regulators of growth factor bioavailability by forming IGFBP-IGF complexes [10]. According to Adamek et al., IGFBPs are also used to supply IGFs in specific tissue sections, restrict the activity of IGFs by depressing the availability of their receptors, and shield them from proteolytic degradation [26]. Moreover, soluble IGFBPs are specific proteins that are capable of interacting with IGFs in extracellular and interstitial fluids of living organisms [40]. In the plasma, 99% of IGFs interact with the family of compulsory proteins, which controls the accessibility of free IGF-1 (fIGF-1) to the tissues. In humans, nearly 80% of circulating IGF-1 is transported by IGFBP-3, a ternary complex comprising one molecule of IGF-1, IGFBP-3, and ALS each [31, 32].

Unbound IGFs and IGFs in binary interactions have short lifespans, they are estimated to last minutes to hours in the circulation. Total IGF estimation in single blood specimens consequently undervalues this dynamic IGF turnover and fails to show the appropriate tissue IGF production, which contributes to the activity of IGF at the cellular level [33, 41].

Another study has reported that IGFBP-1 concentrations are repressed in response to increased insulin levels in obesity, and that low IGFBP-1 concentrations forecast the development of T2D. Visceral adiposity and hepatic steatosis, along with long-lasting inflammation, contribute to the IGF system phenotype in persons with metabolic abnormalities and T2D. The IGF system participates in vascular pathophysiology and other complications and may therefore be a potential therapeutic target [15]. Importantly, the incidental effects of IGF-1 that impact metabolism include blockade of GH and insulin secretion.

The activities of IGF-1 are controlled by IGFBPs. In obesity and metabolic syndrome (MetS), there is foremost dysregulation of IGFBP secretion resulting in changes in the levels of free IGF-1. In T1D, IGF-1 synthesis is significantly reduced, while in T2D various deviations arise in IGF-1 actions such as sensitization to its mitogenic actions in some target tissues, including liver, pancreas, and peripheral tissues [42].

3.IGFs, insulin resistance (IR), and diabetic complications

3.1. IGFs and IR

IR can be defined as a state in which target tissues show a reduction in responsiveness to insulin. Evidence showed that in T1D a reduction in insulin levels in the portal vein results in dysregulation of the GH/IGF/ IGFBP axis [43]. T1D has been associated with hepatic GH resistance and increased production of IGFBP-1 and -2. Decreased levels of IGFBP-3 result in reduced levels of circulating IGF-1 [10, 43].

Pancreatic β-cells secrete insulin in response to an augmented blood glucose level to compensate for the IR state; β-cells increase basal and postprandial secretions of insulin. However, the cells can no longer compensate for IR and fail to respond appropriately to the impairment in glucose disposal [44], which leads to distorted glucose homeostasis and development of hyperglycemia. In turn, the state of hyperglycemia impairs peripheral IR and insulin action [44, 45].

IR is a pathological condition also resulting in decreased efficiency of insulin signaling for blood glucose regulation [44]. It is a key component of MetS. It also increases the risk of various diseases including T2D, cerebrovascular damage, coronary artery disease, and neurodegenerative disorders [46].

Genetic disorders of IR are characterized either by mutations affecting the insulin receptor or defects in post-receptor sites. For example, T2D is associated with the downregulation of peripheral insulin-binding sites and upregulation of tissue-specific IGF binding [21]. Furthermore, evidence suggests that IR, along with the associated hyperglycemia, occurs in classic insulin target organs, and that these conditions are the pathological hallmark of metabolic disorders such as obesity and T2D [46].

A study has investigated the effect of IGF-1 on insulin sensitivity and its relation to T2D. The National Health and Nutrition Examination Survey III reported a higher risk of IR, MetS, and T2D in patients with low serum IGF-1 level [21].

A mice model showed that deletion of hepatic IGF-1 production may result in 80% reduction in IGF-1 concentration and subsequently increased insulin concentration in the blood as well as disorders in blood glucose concentration and glucose clearance [47, 48]. Moreover, supporting evidence by Friedrich et al. showed a negative relationship between IGF-1 levels and IR measured by the homeostasis model assessment of IR [49].

Evidence suggests that the IGF axis may play a role in glucose homeostasis. Rajpathak et al. showed that exogenous administration of IGF-1 decreases serum glucose concentrations and improves insulin sensitivity in individuals with and without T2D [34]. Also, insulin and IGF-1 are capable of increasing glucose uptake and glycogen synthesis and decreasing protein catabolism [42]. IGF-1 has little effect on the adipocyte and mature liver due to a lack of IGF-1 receptors at these sites, but recombinant human IGF-1 has been shown to overwhelm hepatic glucose production via unknown mechanisms, and recombinant human IGF-1 therapy has proved efficacious in patients with severe IR [50].

Deviations in GH and IGF-1 function alter insulin's ability to maintain normal carbohydrate homeostasis [42]. In a mice model, elimination of IGF-1 synthesis in the liver and crossbreeding with mice that overexpress a mutant form of GH that prevents GH activation of its receptor showed that GH is a major determinant of IR in IGF-1-deficient mice [51].

Administration of IGF-1 to normal humans resulted in lower concentrations of glucose; the effect was nearly 1/10th as potent as that induced by insulin. Supporting evidence by Clemmons et al. showed that patients with extreme IR had improved insulin sensitivity and carbohydrate homeostasis after IGF-1 administration [51].

In summary, hepatic IGF-1 production plays a role in the reduction of IGF-1 concentrations, which directly increases concentrations of insulin in the blood and results in elevated blood glucose concentrations and IR [47-49].

3.2. The metabolic link between IGFs and diabetes complications

Insulin regulates cellular energy supply and macronutrient balance and direct anabolic processes of the fed state. It is crucial for the intracellular transport of glucose into insulin-dependent tissues, including skeletal muscle, adipose tissue, and liver [52]. Similarly to insulin, IGF-1 also promotes protein synthesis in skeletal muscles and other tissues. Insulin also appears to have another impact on the metabolism in vascular smooth muscles as there are only receptors for IGF-1 in these tissues [53].

In humans, a study showed that insulin upregulates hepatic GH receptor expression and increases net cell surface receptor availability in the portal circulation. Although GH and insulin have metabolically opposed hormones, insulin has been described to play a role in facilitating the action of GH. In children with T1D, low concentrations of GH-binding protein secondary to low levels of portal insulin have been reported,

which indirectly decrease levels of IGF-1 [16]. The decreased level of IGFBP-1 in T1D may be caused by absolute insulin deficiency. A study in T2D patients suggested that decreased IGFBP-1 concentrations were due to hyperinsulinemia [11, 14].

Insulin levels decrease during fasting to enable mobilization of fatty acids, glycerol from adipose tissue, and amino acids from muscle, but they increase in the fed state [52]. The extent of insulin sensitivity may be predisposed by the composition of the diet, and chronic surplus energy consumption endorses hyperinsulinemia. IR triggers complete stimulation of insulin secretion, triglyceride synthesis, and fat buildup, while insulin receptors are downregulated [53]. Prospective data showed that low levels of IGF-2 may induce the risk of weight gain in T2D patients. This strong inverse association seems to be independent of other risk factors for weight gain and obesity [54].

The effects of fasting on vascular smooth muscle metabolism appear to be similar to the effects of diabetes on vascular metabolism during the early stages of diabetes. The relation of high-fat diets and IR seems to be due to saturated fat and trans-fatty acids because these fatty acids play a role in the development of IR through effects on the composition of membrane lipids [55].

GH acts on IGF-1 secretion, which has metabolic actions of its own and depends on weight status. A study showed that IGF-1 is dependent on body mass index (BMI), with a maximal level at BMI of 30-35 kg/m2. This relation is reflected in severe GH deficiency, indicating that GH-independent IGF-1 secretion represents an imperative metabolic regulator [56].

Infusion of recombinant human IGF-1 in IR patients showed that IGF-1 plays a role in the regulation of cell mass, insulin secretion, and regulation of insulin sensitivity.

The energy-sensing character of a cohesive IGF-1/insulin system controls lipolysis, proteolysis, and IR [56]. Moreover, administration of IGF-1 to patients with IR showed an improvement in glycemic status. Clemmons et al. reported that IGF-1 is associated with lowering blood glucose concentrations and increasing insulin sensitivity in diabetes patients. However, diabetes patients are also sensitive to stimulation of adverse effects in response to IGF-1. IGF-1 coordinately links GH and insulin action and has direct effects on intermediary metabolism [42].

Other studies reported that IGF-1 impacts lipid and glucose metabolism [57], and that its exogenous administration augments insulin sensitivity in healthy adults and T2D patients. Sesti et al. showed that in about 500 patients IGF-1 concentrations were autonomously associated with insulin sensitivity, accounting for 10.8% of its variation [58]. IGF-1 plasma concentrations were associated with a 90.5% decrease in the risk of MetS [58].

In summary, GH, IGF, and insulin have important roles in normal physiology of the body. GH and insulin are metabolically opposed hormones. Insulin has been described to have a permissive role in facilitating the action of GH, and relatively low levels of IGF may increase the risk of weight gain in diabetes patients. Administration of IGF-1 to patients with IR may improve their glycemic status and positively impact lipid and glucose metabolism.

MATERIALS AND METHODS

STUDY DESIGN

Patients: The number of patients was 113, divided into three groups, control group (n=50), NIDDM group (n=32) and IDDM group (n=30). The study was carried out at General hospitals in Babel province, Iraq. Sample size was taken by consecutive manner.

Confirmation of DM: According to the level of Blood sugar, C-peptide and IGF-1 levels to all 3 groups.

Exclusion criteria: Eligible patients should not document with known chronic liver diseases, kidney diseases, thyroid diseases, or using any medications that affect on levels of GH or insulin (e.g. Somatropin, Quinidine, alcohol, etc)

Ethics statement: The study was carried out in compliance with the Declaration of Helsinki principles and was approved by the University of Babylon/College of Pharmacy's Institutional Review Committee. After gaining their verbal consent from participants, the data was collected by a well-trained researcher using a standardized questionnaire in addition to blood samples.

Demographic and clinical variables

Descriptive data for both studied groups were collected by trained researcher following a structured questionnaire. Age, gender, residency, economic and social states and body mass index (BMI).

C-peptid and Insulin like Growth factor-1 levels

C-peptid and Insulin like Growth factor-1(IGF-1)indices were measured by ELISA technique (DiaMetra company, Italy). Each assay was run with known standards (provided with the kit) that were used to determine the quantity of both markers in each sample in ng/ml.

Statistical analysis

Descriptive measures and T-test analysis were used to examine associations and differences in Demographic and clinical variables, C-peptides and IGF-1 markers. The significance level for all analyses was set at a probability (P) of less than or equal to 0.05. All analyses were performed by GraphPad Prism 5.3 for Windows (GraphPad Software, San Diego, CA, USA).

Results

Table 1. sociodemographic data, the information of all studied groups (DM Type 1, DM Type 2 and control).

Parameters	Sub-parameters	Control group N = 50	DM Type 1 group N = 30	DM Type 2 group N = 32
Age	18-25 yrs	13	18	0
	25-35 yrs	8	8	3
	36-45 yrs	12	6	6
	46-55 yrs	12	7	9
	> 55 yrs	5	1	14
Sex	Male	22	19	18
	Female	28	11	14
Socioeconomic state	Low	10	11	10
	Medium	17	11	12
	High	23	8	10
Educational Level	Elementary	6	11	7
	Secondary	16	39	13
	Bachelor or >	28	12	12

Occupation	Free job	26	17	16
	Employee	24	13	16

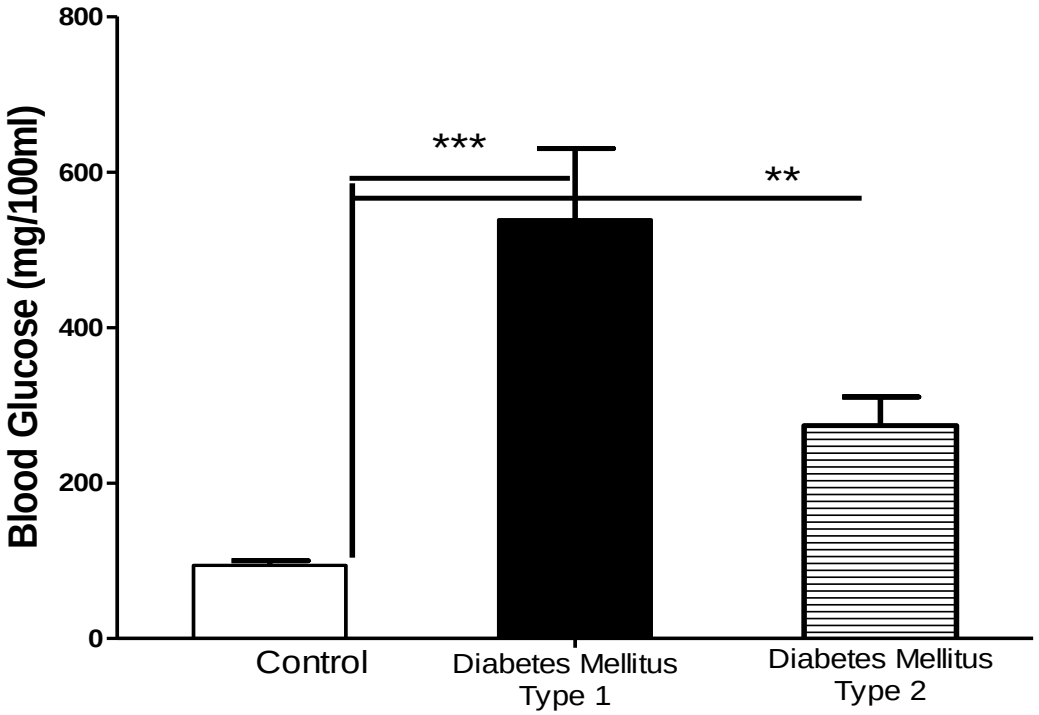


Figure 1: Variation in Blood sugar concentration (mg/100ml) among patients with Diabetes (Type 1 and Type 2) and control group. The number of asterisks (***) and (**) correspond to the level of the statistical significance ($P < 0.001$ and $P < 0.01$ respectively).

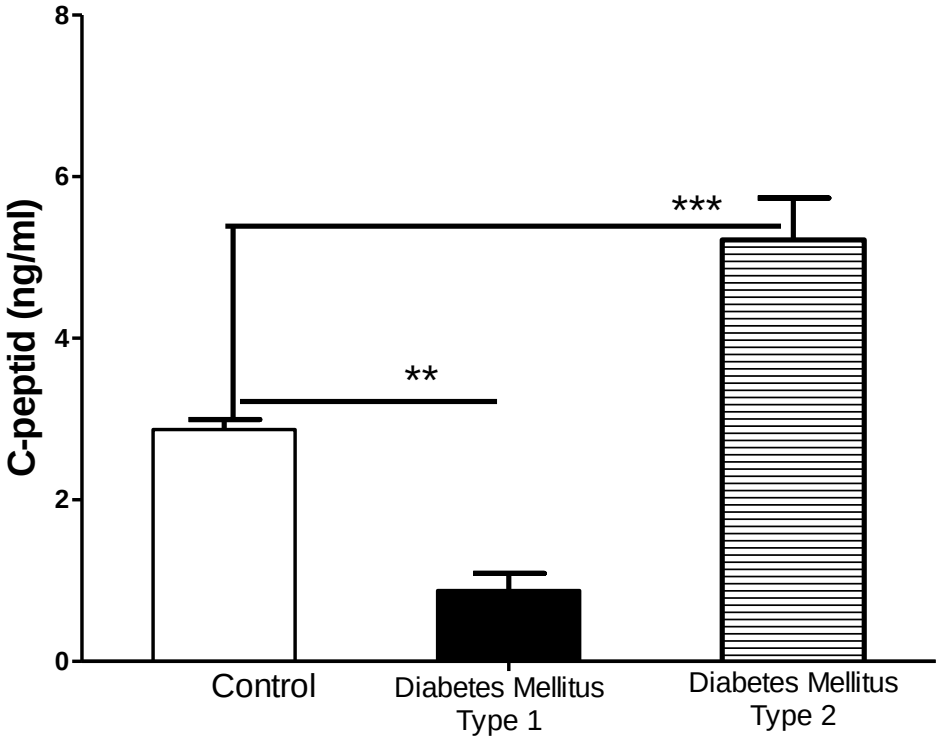


Figure 2: Variation in C-peptide concentration (ng/ml) among patients with Diabetes (Type 1 and Type 2) and control group. The number of asterisks (***) and (**) correspond to the level of the statistical significance ($P < 0.001$ and $P < 0.01$ respectively).

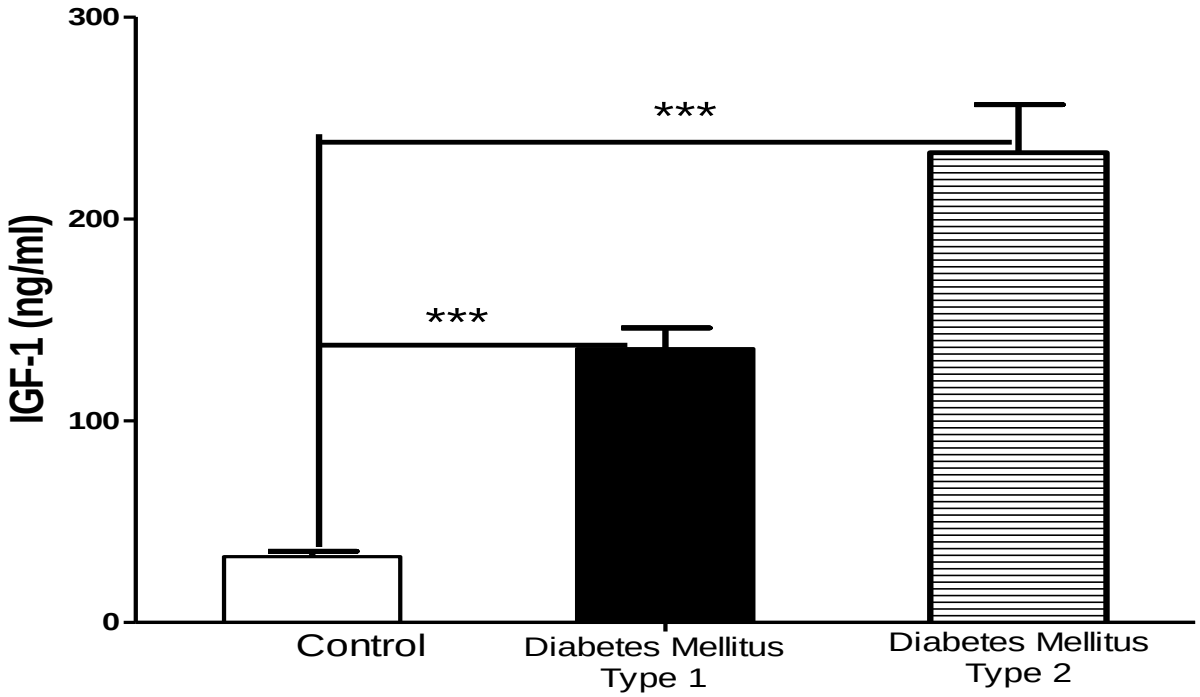


Figure 3: Variation in IGF-1 concentration (ng/ml) among patients with Diabetes (Type 1 and Type 2) and control group. The number of asterisks (***) correspond to the level of the statistical significance ($P < 0.001$).

5.Conclusions and recommendations

The IGF system is a very important endogenous mechanism recruited daily for beneficial action in cardiovascular and metabolic health disorders, IR, and diabetes complications. The role of IGF-1 in the development of IR and diabetes complications has already been described. A positive relationship between the circulating levels of IGF-1 (IGF-ItoIGFBP-3 ratio) and MetS, diabetes, and CVD has been reported. It may thus be considered that high circulating levels of IGF-1 are associated with the development of MetS and raise the risk of CVD and diabetes complications.

Cellular senescence reduces vascular endothelial proliferation. Adhesion plays an essential role in the progression of macrovascular disease. High IGF-1 availability may defend against the onset of CVD and glucose intolerance in diabetes patients. Moreover, IGF-1 increases nitric oxide production and potassium ion channel opening in cardiovascular physiology, both of which improve the weakened small vessel function linked with low IGF-1 concentrations in patients with cardiovascular syndrome.

Therefore, the IGF system is involved in vascular pathophysiology during progression to and protection from vascular complications; it has also been implicated in metabolic abnormalities. Therefore, the IGF system may have a therapeutic potential in reducing the risk of the development and progression of vascular complications in diabetes patients. Further studies should focus on the role of IGF in diabetes complications and emphasis the mechanism of the system to tackle disease progression and reduce diabetes-related complications in large cohorts of patients.

6- Abbreviations

- ALS acid-labile subunit
- BRB blood-retinal barrier
- CVD cardiovascular disease
- DN diabetic nephropathy
- DNP diabetic neuropathy
- DR diabetic retinopathy
- ESRD end-stage renal disease
- fIGF free insulin-like growth factor
- GH growth hormone
- GHR growth hormone receptor
- IGF insulin-like growth factor
- IGF-1R/2R insulin-like growth factor 1 receptor / 2 receptor
- IGFBP insulin-like growth factor binding protein
- IR insulin resistance
- LDL low-density lipoprotein
- MetS metabolic syndrome
- T1D type 1 diabetes mellitus
- T2D type 2 diabetes mellitus
- VEGF vascular endothelial growth factor

7- References

1. Brissenden JE, Ullrich A, Francke U. Human chromosomal mapping of genes for insulin-like growth factors I and II and epidermal growth factor. Nature 1984. 310(5980):781-784. [PubMed] [Google Scholar]

2. Le Roith D, Scavo L, Butler A. What is the role of circulating IGF-I? Trends Endocrinol Metab 2001. 12(2):48-52. [PubMed] [Google Scholar]

3. Hwa V, Oh Y, Rosenfeld RG. The insulin-like growth factor-binding protein (IGFBP) superfamily. Endocr Rev 1999. 20(6):761-787. [PubMed] [Google Scholar]

4. Romero CJ, Pine-Twaddell E, Sima DI, Miller RS, He L, Wondisford F, et al.. Insulin-like growth factor 1 mediates negative feedback to somatotroph GH expression via POU1F1/CREB binding protein interactions. Mol Cell Biol 2012. 32(21):4258-4269. [PMC free article] [PubMed] [Google Scholar]

5. Roelfsema V, Clark RG. The growth hormone and insulin-like growth factor axis: its manipulation for the benefit of growth disorders in renal failure. J Am Soc Nephrol 2001. 12(6):1297-1306. [PubMed] [Google Scholar]

6. Wang Y, Zhang H, Cao M, Kong L, Ge X. Analysis of the value and correlation of IGF-1 with GH and IGFBP-3 in the diagnosis of dwarfism. Exp Ther Med 2019. 17(5):3689-3693. [PMC free article] [PubMed] [Google Scholar]

7. Bae JH, Song DK, Im SS. Regulation of IGFBP-1 in metabolic diseases. J Lifestyle Med 2013. 3(2):73. [PMC free article] [PubMed] [Google Scholar]

8. David A, Hwa V, Metherell LA, Netchine I, Camacho-Hübner C, Clark AJ, Rosenfeld RG, Savage MO. Evidence for a continuum of genetic, phenotypic, and biochemical abnormalities in children with growth hormone insensitivity. Endocr Rev 2011. 32(4):472-497. [PubMed] [Google Scholar]

9. Blum WF, Alherbish A, Alsagheir A, El Awwa A, Kaplan W, Koledova E, Savage MO. The growth hormone–insulin-like growth factor-I axis in the diagnosis and treatment of growth disorders. Endocr Connect 2018. 7(6):R212-R222. [PMC free article] [PubMed] [Google Scholar]

10. Bäck K.. Interaction between insulin and IGF-I receptors in insulin sensitive and insulin resistant cells and tissues. Linköping University Electronic Press, 2011.

11. Lu S, Purohit S, Sharma A, Zhi W, He M, Wang Y, Li C, She J. Serum insulin-like growth factor binding protein 6 (IGFBP6) is increased in patients with type 1 diabetes and its complications. Int J Clin Exp Med 2012. 5(3):229. [PMC free article] [PubMed] [Google Scholar]

12. Palakawong P, Arakaki R. Diabetic ketoacidosis in acromegaly: A case report. Endocr Pract 2012. 27:1-15. [PubMed] [Google Scholar]

13. Janssen JA, Lamberts SW. The role of IGF-I in the development of cardiovascular disease in type 2 diabetes mellitus: is prevention possible? Eur J Endocrinol 2002. 146(4):467-477. [PubMed] [Google Scholar]

14. Gu T, Falhammar H, Gu HF, Brismar K. Epigenetic analyses of the insulin-like growth factor binding protein 1 gene in type 1 diabetes and diabetic nephropathy. Clin Epigenetics 2014. 6(1):10. [PMC free article] [PubMed] [Google Scholar]

15. Lewitt M, Dent M, Hall K. The insulin-like growth factor system in obesity, insulin resistance and type 2 diabetes mellitus. J Clin Med 2014. 3(4):1561-1574. [PMC free article] [PubMed] [Google Scholar]

16. Nambam B, Schatz D. Growth hormone and insulin-like growth factor-I axis in type 1 diabetes. Growth Horm IGF Res 2018. 38: 49-52. [PubMed] [Google Scholar]

17. Khan ZA, Chakrabarti S. Growth factors in proliferative diabetic retinopathy. Exp Diabesity Res 2003. 4(4):287-301. [PMC free article] [PubMed] [Google Scholar]

18. Bazzaz JT, Amoli MM, Taheri Z, Larijani B, Pravica V, Hutchinson IV. TGF-beta1 and IGF-I gene variations in type 1 diabetes microangiopathic complications. J Diabetes Metab Disord 2014. 13(1):45. [PMC free article] [PubMed] [Google Scholar]

19. Kummer A, Pulford BE, Ishii DN, Seigel GM. Des (1-3) IGF-1 treatment normalizes type 1 IGF receptor and phospho-Akt (Thr 308) immunoreactivity in predegenerative retina of diabetic rats. Int J Exp Diabesity Res 2003. 4(1):45-57. [PMC free article] [PubMed] [Google Scholar]

20. Neamtu MC, Avramescu ET, Marcu IR, Turcu-stiolica A, Boldeanu MV, Neamtu OM, Tudorache S, Miulescu RE. The correlation between insulin-like growth factor with glycemic control, glomerular filtration rate, blood pressure, hematological changes or body mass index in patients with type 2 diabetes mellitus. Rom J Morphol Embryol 2017. 58:857-861. [PubMed] [Google Scholar]

21. Thrailkill KM. Insulin-like growth factor-I in diabetes mellitus: its physiology, metabolic effects, and potential clinical utility.Diabetes Technol Ther 2000. 2(1):69-80. [PubMed] [Google Scholar]

22. Venkatasubramanian G, Chittiprol S, Neelakantachar N, Naveen MN, Thirthall J, Gangadhar BN, Shetty KT. Insulin and insulin-like growth factor-1 abnormalities in antipsychotic-naive schizophrenia. Am J Psychiatry 2007. 164(10):1557-1560. [PubMed] [Google Scholar]

23. Knott RM. Insulin-like growth factor type 1 - friend or foe? BMJ Publishing Group Ltd, 1998. [PMC free article] [PubMed]

24. Roith DL. The insulin-like growth factor system. Exp Diabesity Res 2003. 4(4):205-212. [PMC free article] [PubMed] [Google Scholar]

25. Retnakaran R. The insulin-like growth factor axis: a new player in gestational diabetes mellitus? Diabetes 2016. 65(11):3246-3248. [PubMed] [Google Scholar]

26. Adamek A, Kasprzak A. Insulin-like growth factor (IGF) system in liver diseases. Int J Mol Sci 2018. 19(5):1308. [PMC free article] [PubMed] [Google Scholar]

27. Arcaro A. Targeting the insulin-like growth factor-1 receptor in human cancer. Front Pharmacol 2013. 4:30. [PMC free article] [PubMed] [Google Scholar]

28. Sima AA, Li ZG, Zhang W. The insulin-like growth factor system and neurological complications in diabetes. Exp Diabesity Res 2003. 4(4):235-256. [PMC free article] [PubMed] [Google Scholar]

29. Skalkidou A, Petridou E, Papathoma E, Salvanos H, Kedikoglou S, Chrousos G, Trichopoulos D. Determinants and consequences of major insulin-like growth factor components among full-term healthy neonates. Cancer Epidemiol Biomarkers Prev 2003. 12(9):860-865. [PubMed] [Google Scholar]

30. Bajpai A, Menon P. Insulin like growth factors axis and growth disorders. Indian J Pediatr 2006. 73(1):67-71. [PubMed] [Google Scholar]

31. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone.Mol Pathol 2001. 54(5):311. [PMC free article] [PubMed] [Google Scholar]

32. Ishii DN, Lupien SB. Insulin-like growth factor replacement therapy for diabetic neuropathy: Experimental basis. Exp Diabesity Res 2003. 4(4):257-269. [PMC free article] [PubMed] [Google Scholar]

33. Kim HS, Rosenfeld RG, Oh Y. Biological roles of insulin-like growth factor binding proteins (IGFBPs). Exp Mol Med 1997. 29(2):85. [Google Scholar]

34. Rajpathak SN, He M, Sun Q, Kaplan RC, Muzumdar R, Rohan TE, Gunter MJ, Pollak M, Kim M, Pessin JE, et al.. Insulin-like growth factor axis and risk of type 2 diabetes in women. Diabetes 2012. 61(9):2248-2254. [PMC free article] [PubMed] [Google Scholar]

35. Bachner-Melman R, Zohar AH, Nemanov L, Heresco-Levy U, Gritsenko I, Ebstein RP. Association between the insulin-like growth factor 2 gene (IGF2) and scores on the eating attitudes test in nonclinical subjects: a family-based study. Am J Psychiatry 2005. 162(12):2256-2262. [PubMed] [Google Scholar]

36. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol 2014. 6(1):a009191. [PMC free article] [PubMed] [Google Scholar]

37. Leung KC, Johannsson G, Leong GM, Ho KK. Estrogen regulation of growth hormone action. Endocr Rev 2004. 25:693-721. [PubMed] [Google Scholar]

38. Berryman DE, Glad CA, List EO, Johannsson G. The GH/IGF-1 axis in obesity: Pathophysiology and therapeutic considerations. Nat Rev Endocrinol 2013. 9:346-356. [PubMed] [Google Scholar]

39. Dynkevich YR, Rother KI, Whitford I, Qureshi S, Galiveeti S, Szulc AL, Danoff A, Breen TL, Kaviani N, Shanik MH, et al.. Tumors, IGF-2, and hypoglycemia: Insights from the clinic, the laboratory, and the historical archive. Endocr Rev 2013. 34:798-826. [PubMed] [Google Scholar]

40. Kostecka Z, Blahovec J. Animal insulin-like growth factor binding proteins and their biological functions. Vet Med (Praha) 2002. 47(2/3):75-84. [Google Scholar]

41. Ahmed RL, Thomas W, Schmitz KH. Interactions between insulin, body fat, and insulin-like growth factor axis proteins.Cancer Epidemiol Biomarkers Prev 2007. 16(3):593-597. [PubMed] [Google Scholar]

42. Clemmons DR. Metabolic actions of insulin-like growth factor-I in normal physiology and diabetes. Endocrinol Metab Clin North Am 2012. 41:425-443. [PMC free article] [PubMed] [Google Scholar]

43. Gutefeldt K, Hedman CA, Thyberg IS, Bachrach-Lindström M, Spangeus A, Arnqvist HJ. Dysregulated growth hormone insulin-like growth factor-1 axis in adult type 1 diabetes with long duration. Clin Endocrinol 2018. 89:424-430. [PubMed] [Google Scholar]

44. Fu Z, R Gilbert E, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. Curr Diabetes Rev 2013. 9(1):25-53. [PMC free article] [PubMed] [Google Scholar]

45. Fernandez AM, Kim JK, Yakar S, Dupont J, Hernandez-Sanchez C, Castle AL, Filmore J, Shulman GI, Roith DL. Functional inactivation of the IGF-I and insulin receptors in skeletal muscle causes type 2 diabetes. Genes Dev 2001. 15(15):1926-1934. [PMC free article] [PubMed] [Google Scholar]

46. Djiogue S, Kamdje AH, Vecchio L, Kipanyula MJ, Farahna M, Aldebasi Y, Etet PF. Insulin resistance and cancer: the role of insulin and IGFs. Endocr Relat Cancer 2013. 20(1):R1-R17. [PubMed] [Google Scholar]

47. Yakar S, Liu JL, Fernandez AM, Wu Y, Schally AV, Frystyk J, Chernausek SD, Mejia W, Roith DL. Liver-specific igf-1 gene deletion leads to muscle insulin insensitivity. Diabetes. 2001. 50(5):1110-1118. [PubMed] [Google Scholar]

48. Yakar S, Kim H, Zhao H, Toyoshima Y, Pennisi P, Gavrilova O, Leroith D. The growth hormone-insulin like growth factor axis revisited: lessons from IGF-1 and IGF-1 receptor gene targeting. Pediatr Nephrol 2005. 20(3):251-254. [PubMed] [Google Scholar]

49. Friedrich N, Thuesen B, Jørgensen T, Juul A, Spielhagen C, Wallaschofksi H, Linneberg A. The association between IGF-I and insulin resistance: a general population study in Danish adults. Diabetes Care 2012. 35(4):768-773. [PMC free article] [PubMed] [Google Scholar]

50. McDonald A, Williams RM, Regan FM, Semple RK, Dunger DB. IGF-I treatment of insulin resistance. Eur J Endocrinol 2007. 157(Suppl 1):S51-S56. [PubMed] [Google Scholar]

51. Clemmons DR. The relative roles of growth hormone and IGF-1 in controlling insulin sensitivity. J Clin Invest 2004. 113(1):25-27. [PMC free article] [PubMed] [Google Scholar]

52. Loh K, Zhang L, Brandon A, Wang Q, Begg D, Qi Y, Fu M, Kulkarni R, Teo J, Baldock P, et al.. Insulin controls food intake and energy balance via NPY neurons. Mol Metab 2017. 6(6):574-584. [PMC free article] [PubMed] [Google Scholar]

53. Dahlkvist HH. Insulin and IGF-1 as Critical Metabolic Regulators. Endocrinol Metab Syndr 2015. 4:1. [Google Scholar]

54. Heald AH, Kärvestedt L, Anderson SG, McLaughlin J, Knowles A, Wong L, Grill V, Cruickshank JK, White A, Gibson JM, Brismar K. Low insulin-like growth factor-II levels predict weight gain in normal weight subjects with type 2 diabetes. Am J Med 2006. 119(2):167.e9-e15. [PubMed] [Google Scholar]

55. Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. Diabetes 2012. 61(6):1315-1322. [PMC free article] [PubMed] [Google Scholar]

56. Kreitschmann-Andermahr I, Suarez P, Jennings R, Evers N, Brabant G. GH/IGF-I regulation in obesity–mechanisms and practical consequences in children and adults. Horm Res Paediatr 2010. 73(3):153-160. [PubMed] [Google Scholar]

57. Le Roith D. Seminars in medicine of the Beth Israel Deaconess Medical Center. insulin-like growth factors. N Engl J Med 1997. 336: 633-640. [PubMed] [Google Scholar]

58. Sesti G, Sciacqua A, Cardellini M, Marini MA, Maio R, Vatrano M, Succurro E, Lauro R, Federici M, Perticone F. Plasma concentration of IGF-I is independently associated with insulin sensitivity in subjects with different degrees of glucose tolerance. Diabetes Care 2005. 28(1):120-125. [PubMed] [Google Scholar]

59. Sharma A, Purohit S, Sharma S, Bai S, Zhi W, Ponny SR, Hopkins D, Steed L, Bode B, Anderson SW, She JX. IGF-binding proteins in type-1 diabetes are more severely altered in the presence of complications. Front Endocrinol 2016. 7:2. [PMC free article] [PubMed] [Google Scholar]

60. Kielczewski JL, Calzi SL, Shaw LC, Cai J, Qi X, Ruan Q, Wu L, Liu L, Hu P, Chan-Ling T, et al.. Free insulin-like growth factor binding protein-3 (IGFBP-3) reduces retinal vascular permeability in association with a reduction of acid sphingomyelinase (ASMase). Invest Ophthalmol Vis Sci 2011. 52(11):8278-8286. [PMC free article] [PubMed] [Google Scholar]

61. Zhang J, Zhang L, Quan L, Qi W, Jiang Y, Jiang S. Correlation of retinopathy with serum levels of growth hormones and insulin-like growth factor-1 in patients with diabetic retinopathy. Int J Clin Exp Med 2017. 10(1):1325-1329. [Google Scholar]

62. Wang H, Xu J, Chen J, Little PJ, Zheng W. Role of IGF-1 signaling in the pathology of diabetic retinopathy. Ther Targets Neurol Dis 2015. 2. [Google Scholar]

63. Tepper OM, Galiano RD, Capla JM, Kalka C, Gagne PJ, Jacobowitz GR, Levine JP, Gurtner GC. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. Circulation 2002. 106(22):2781-2786. [PubMed] [Google Scholar]

64. Bach LA. Endothelial cells and the IGF system. J Mol Endocrinol 2014. 54(1):R1-R13. [PubMed] [Google Scholar]

65. Frystyk J, Ledet T, Moller N, Flyvbjerg A, Orskov H. Cardiovascular disease and insulin-like growth factor 1. Circulation 2002. 106 (8):893-895. [PubMed] [Google Scholar]

66. Conti E, Musumeci MB, De Giusti M, Dito E, Mastromarino V, Autore C, Volpe M. IGF-1 and atherothrombosis: relevance to pathophysiology and therapy. Clin Sci (Lond) 2011. 120(9):377-402. [PubMed] [Google Scholar]

67. Piccioli L, Arcopinto M, Salzano A, D'Assante R, Schiavo A, Stagnaro FM, Lombardi A, Panicara V, Valente P, Vitale G, et al.. The impairment of the growth hormone/insulin-like growth factor 1 (IGF-1) axis in heart failure: A possible target for future therapy. Monaldi Arch Chest Dis 2018. 88(3):975. [PubMed] [Google Scholar]

68. Wallander M, Norhammar A, Malmberg K, Öhrvik J, Rydén L, Brismar K. Insulin-like growth factor binding protein 1 predicts cardiovascular morbidity and mortality in patients with acute myocardial infarction and type 2 diabetes. Diabetes Care 2007. 30(9):2343-2348. [PubMed] [Google Scholar]

69. Komamura K, Miyatake K, Hanatani A, Hashimura K, Kimu C, Ueda H. Insulin-like growth factor-1 improves cardiac function and symptoms in the patients on the waiting list for transplantation with dilated cardiomyopathy. Clinical and Basic Research in Heart Failure (M). The 69th Annual Scientific Meeting of the Japanese Circulation Society. Circulation 2005. 69:130. [Google Scholar]

70. Barton J, Hindmarsh P, Preece M. Serum insulin-like growth factor 1 in congenital heart disease. Arch Dis Child 1996. 75(2):162-163. [PMC free article] [PubMed] [Google Scholar]

71. Watkins P, Thomas P. Diabetes mellitus and the nervous system. J Neurol Neurosurg Psychiatry 1998. 65(5):620-632. [PMC free article] [PubMed] [Google Scholar]

72. Maji D, Singh A. Clinical trial of D-400, a herbomineral preparation in diabetes mellitus. J Diabetic Assoc India 1995. 35(1):1-4. [Google Scholar]

73. Zhuang HX, Wuarin L, Fei ZJ, Ishii DN. Insulin-like growth factor (IGF) gene expression is reduced in neural tissues and liver from rats with non-insulin-dependent diabetes mellitus, and IGF treatment ameliorates diabetic neuropathy. J Pharmacol Exp Ther 1997. 283(1):366-374. [PubMed] [Google Scholar]

74. Friedrich N, Thuesen B, Jorgensen T, Juul A, Spielhagen C, Wallaschofksi H, Linneberg A. The association between IGF-I and insulin resistance: a general population study in Danish adults. Diabetes Care 2012. 35(4):768-773. [PMC free article] [PubMed] [Google Scholar]

75. Malone JI. Diabetic central neuropathy: CNS damage related to hyperglycemia. Diabetes 2016. 65(2):355-357. [PubMed] [Google Scholar]

76. American Diabetes Association . Standards of medical care in diabetes-2015 abridged for primary care providers. Clin Diabetes 2015. 33(2):97. [PMC free article] [PubMed] [Google Scholar]

77. Pugliese G. Updating the natural history of diabetic nephropathy. Acta Diabetol 2014. 51(6):905-915. [PubMed] [Google Scholar]

78. Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. Kidney Int Suppl 2018. 8(1):2-7. [PMC free article] [PubMed] [Google Scholar]

79. Nazar CM. Diabetic nephropathy; principles of diagnosis and treatment of diabetic kidney disease. J Nephropharmacol 2014. 3(1):15. [PMC free article] [PubMed] [Google Scholar]

80. Kamenicky P, Mazziotti G, Lombes M, Giustina A, Chanson P. Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications. Endocr Rev 2014. 35(2):234-281. [PubMed] [Google Scholar]

81. Carroll PV, Christ ER, Umpleby AM, Gowrie I, Jackson N, Bowes SB, Hovorka R, Croos P, Sönksen PH, Russell-Jones DL. IGF-I treatment in adults with type 1 diabetes: effects on glucose and protein metabolism in the fasting state and during a hyperinsulinemiceuglycemic amino acid clamp.