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"The Assessment of The Changes in The Level of C-peptide in Obese Subjects"

A graduation project submitted to the college of pharmacy /Babylon University as partial fulfillment of the requirement of the BSc degree in pharmacy

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بسِـــــمِ اللـَّهِ الرَّحْمَـٰنِ الرَّحِيمِ

يرْفعِ اللَّه اللذِينَ آمَنوُا مِنكُمْ وَاللذِينَ أوُتوُا الْعِلْمَ دَرَجَاتٍ واللَّه بِمَا تعْمَلوُنَ خَبيِر

صدق الله العلي العظيم

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الخلفية

يتزايد انتشار السمنة بين عامة السكان. كنا نعتزم العثور على العوامل المرتبطة بإمكانية الحفاظ على إفراز الأنسولين الداخلي لدى الأفراد. تحدد الدراسة تأثير مؤشر كتلة الجسم على إفراز الببتيد C في الأشخاص الذين يعانون من السمنة المفرطة وتقارن النتائج مع المجموعة الضابطة.

الطُرق

قمنا بتقييم العلاقة المحتملة بين مؤشر كتلة الجسم وحالة وظيفة الخلية بيتا كمستويات الببتيد C في إجمالي 102 موضوعًا مقسمة إلى مجموعتين، المجموعة التي تعاني من السمنة المفرطة مع مؤشر كتلة الجسم> 30 (ن = 52) والمجموعة الضابطة (ن = 50). . تمت متابعة المشاركين من خلال استبيان تم إجراؤه بواسطة فاحصين مدربين تدريباً جيداً. تم تقييم-C الببتيد و IGF-1في كلا المجموعتين.

النتائج

الأشخاص الذين لديهم مؤشر كتلة الجسم أعلى تم تقديم مستويات عالية من الببتيد C و IGF-1في المصل لديهم مقارنة بالمجموعة الضابطة، على الرغم من وجود فروق ذات دلالة إحصائية في مستويات السكر في الدم عند التشخيص بين المجموعات المدروسة.

الخاتمة

ارتفاع مؤشر كتلة الجسم، المرتبط بمستويات معززة من مستويات الببتيد C مع زيادة في - IGFمما قد يشير إلى تأثير سلبي لوزن الجسم الزائد على الحفاظ على وظيفة خلايا بيتا المتبقية على المدى الطويل.

Abstract

Background

The prevalence of obesity is increasing in general population. We intended to find factors associated with the possibility of preserving endogenous insulin secretion in individuals. The study determines the influence of BMI on C-peptide secretion in obese subjects and compares the results with the control group.

Methods

We assessed the possible relationship between body mass index and β-cell function status as C-peptide levels in total 102 subjects divided into two groups, the obese group with BMI> 30 (n=52) 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

Subjects with higher BMI presented with high serum C-peptide and IGF-1 levels compared with the control group, despite statistically insignificant differences in blood sugar levels at diagnosis between the studied groups.

Conclusion

Higher BMI, associated with enhanced levels of C-peptide levels combined with an increase in IGF-which may indicate a negative effect of excess body weight on the long term preservation of residual β-cell function.

Keywords: Obesity, BMI, C-peptide, IGF-1, residual beta cell function

INTRODUCTION

Obesity

Obesity is a pathological condition in which excess body fat accumulated, leading adverse effects on health and life expectancy. [1] It is a chronic disorder with complex interaction between genetic and environmental factors. It characterized by high cholesterol, fatty acid levels; imbalance in metabolic energy; insulin desensitization; lethargy, gallstones; high blood pressure; shortness of breath; emotional and social problems; and excessive adipose mass accumulation with hyperplasia and hypertrophy. [2] Pathological obesity is associated with several

secondary commodities like heart disease, type 2 diabetes, breathing difficulties during sleep, cancer and osteoarthritis. [1] It is most commonly caused by a combination of excessive dietary calories, lack of physical activity, and genetic susceptibility. Evidence to support this view is that some obese people eat little yet gain weight due to slow metabolic rate. [3,4] The primary treatment for obesity are dieting and physical exercise. To supplement this, or in case of failure, anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption. In severe cases, surgery is performed or an intragastric balloon is placed to reduce stomach volume and/or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food [5,6].

Worldwide prevalence:

Obesity is one of the leading preventable causes of death worldwide. [7] Currently more than 1 billion adults are overweight and at least 300 million of them are clinically obese. Current obesity levels range from below 5% in China, Japan and certain African nations, to over 75% in urban Samoa. Childhood obesity is already epidemic in some areas and on the rise in others. An estimated 17.6 million children under five yr. age are estimated to be overweight worldwide. According to the US Surgeon General, in the USA the number of overweight children has doubled and the number of overweight adolescents has trebled since 1980. The prevalence of obese children aged 6-to-11 years has more than doubled since the 1960s. Obesity prevalence in youths aged 12-17 has increased dramatically from 5% to 13% in boys and from 5% to 9% in girls between 1966-70 and 1988-91 in the USA. The problem is global and increasingly extends into the developing world: In Thailand the prevalence of obesity in 5-to-12 year olds children rose from12.2% to 15-6% in just two years. Obesity accounts for 2-6% of total health care costs in several developed countries. The true costs are undoubtedly much greater as not all obesity-related conditions are included in the calculations. [8] In

the United States obesity is estimated to cause an excess 111,909 to 365,000 death per year, while

1 million (7.7%) of deaths in the European Union are attributed to excess weight. [9,10]

Classification:

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health. [11] It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors. [12] BMI is closely related to both percentage body fat and total body fat. [13] In children a healthy weight varies with age and sex. Obesity in children and adolescents is defined not as an absolute number but in relation to a historical normal group, such that obesity is a BMI greater than the 95th percentile. The reference data that these percentiles are based on are from 1963 to 1994, and thus have not been affected by the recent increases in weight. [7,14,15] At onset, higher BMI is associated with higher C-peptide level, which may indicate to be one of the favorable factors involved in preserving residual β-cell function.

The most commonly used definitions, established by the World Health Organization in 1997 and published in 2000 provide the values listed in the table at right. [2] The surgical literature breaks down "class III" obesity into further categories whose exact values are still disputed. [16] As Asian populations develop negative health consequences at a lower BMI than Caucasians, some nations have redefined obesity; the Japanese have defined obesity as any BMI greater than 25 [17] while China uses a BMI of greater than 28. [18]

Table 1: Classification of obesity based on BMI

BMI	Classification
< 18.5	underweight
18.5–24.9	normal weight
25.0–29.9	Overweight
30.0–34.9	class I obesity (Obese)
35.0–39.9	class II obesity (Sever obesity)
≥ 40.0	class III obesity (Morbid obesity)
≥ 40- 50	Super obese

Mechanisms:

Obesity is majorly responsible for metabolic dysfunction involving lipid and glucose. It also facilitates secondary complications like cardiac, liver, intestinal, pulmonary, endocrine, and reproductive dysfunctionings. The provoked inflammatory, insulinresistant, hypertensive, and thrombotic-promoting adipokines, which are atherogenic are counter-balanced by anti-inflammatory and anti-atherogenic adipocyte hormones such as adiponectin, visfatin, and acylation-stimulating protein, whereas certain actions of leptin and resistin are pro-atherogenic. [19] It occurs due to imbalance between food intake and energy expenditure. Possible involvement of NPY (Neuro Peptide Y), MCH

(Melanocortin hormone), AGRP (Agouti gene related peptide), Orexin-A and –B, Galanin, α-MSH (α-Melanin stimulating hormone), CRF (corticotrophin releasing hormone), CART (caffeine and amphetamine releasing hormone), Glucagonlike peptide-1 (GLP-1), CCK (coli cysto kine), 5-HT (5-Hydroxy triptamine), insulin, and leptin found to occur during regulation of food intake. [20,21] Moreover, it also contributes to immune dysfunction from the effects of its inflammatory adipokine secretion; and the worsening of metabolic syndrome. Molecular and genetic studies of animal models have identified numerous genes that may cause or contribute to the development of obesity. They have also provided significant insight into the peripheral and central regulating cascades like (i) Peripheral: insulin, leptin, gheralin, CCK, 5- HT [20] and (ii) Central: NPY, AGRP, α-MSH, Orexin, CART, MCH [21] that control energy intake and expenditure. [Fig 1] Genetic studies of families and populations have generated useful information on genes and mutations associated with or linked to obesity, body fat distribution, and other relevant phenotypes. [22]

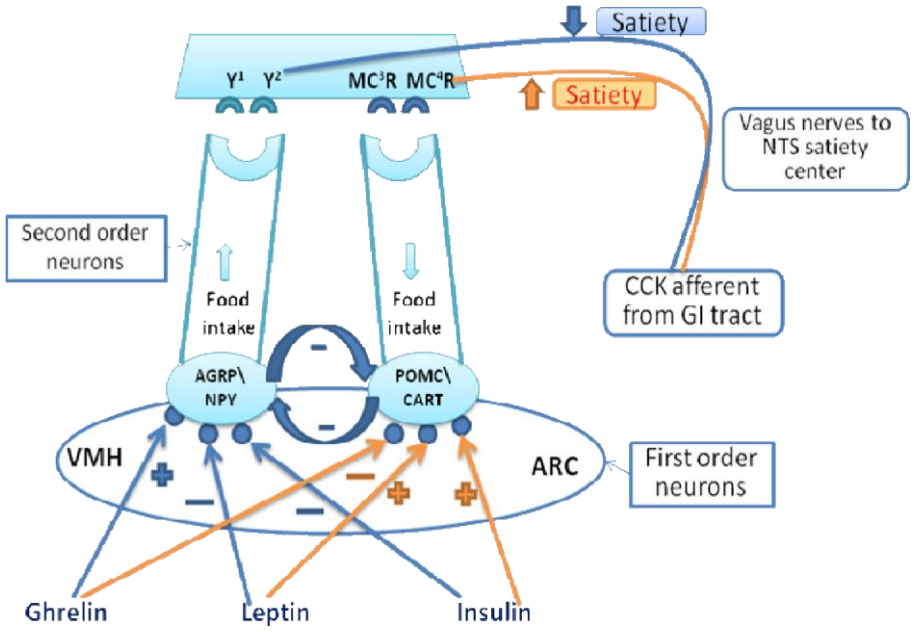

Figure: : VMH (Ventro medial hypothalamus), ARC (Arcuate nucleus), NPY (Neuro peptide-Y), AGRP (Agouti gene related peptide), POMC (Propio melanocortin), CART (caffeine and amphetamine related peptide), CCK (Cholecystokines), GI (Gastro intestinal), Y1,2 (NPY 1,2 receptor), MC 3,4R (Melanocortin receptor)

Fig 1: Mechanism of Obesity

Co-morbidities associated with obesity:

Obesity increases the risk of several physical and mental conditions. The co-morbidities are most commonly shown in metabolic syndrome, which includes: diabetes mellitus (type 2), high blood pressure, high blood cholesterol, and high triglyceride levels. [23] Complications are either directly caused by obesity or indirectly related through mechanisms sharing a common cause such as a poor diet or a sedentary lifestyle. Excess body fat underlies 64% of cases of diabetes in men and 77% of cases in women. [24] Health consequences fall into two broad categories: those attributable to the effects of increased fat mass (such as osteoarthritis, obstructive sleep apnea, social stigmatization) and those due to the increased number of fat cells (diabetes, cancer, cardiovascular disease, non-alcoholic fatty liver disease). [24,25] Increases in body fat alter the body's response to insulin, potentially leading to insulin resistance. It also creates a pro-inflammatory state, Shoelson SE and a prothrombotic state. [24,26] Large-scale American and European studies have found that mortality risk is lowest at a BMI of 22.5–25 kg/m2 in non-smokers and at 24– 27 kg/m2 in current smokers, with risk increasing along with changes in either direction. [27,28] The risk of obesity with higher co-morbidities are as follows.

Cardiology - ischemic heart disease, angina and myocardial infarction, congestive heart failure, high blood pressure, abnormal cholesterol levels, deep vein thrombosis and pulmonary embolism. [1]

Endocrinology - Diabetes mellitus, polycystic ovarian syndrome, menstrual disorders, infertility, complications during pregnancy, birth defects and intrauterine fetal death. [1]

Neurology - Stroke, neuralgia parenthetical, migraines, carpal tunnel syndrome, dementia, idiopathic intracranial hypertension and multiple sclerosis. [29]

Psychiatry - Depression in women and social stigmatization. [1]

Rheumatology and Orthopaedics - Gout, poor mobility, osteoarthritis and low back pain. [30]

Gastrointestinal – Gastroesophageal reflux disease, fatty liver disease and cholelithiasis (gallstones). [1]

Respirology - Obstructive sleep apnea, obesity hypoventilation syndrome, asthma and increased complications during general anesthesia [Fig 2]. [1]

Fig 2: Co-Morbidities associated with Obesity

Factors modulating obesity:

1. **Age -** Childhood obesity is a risk factor for adulthood obesity, Body fat content increases during adulthood, the maximal rates of overweight and obesity attained from 55 to 65 yr. [31]

2. **Sex** - Women have more body fat. The differences in prevalence of obesity vary in populations or among ethnic groups. Obese men often have low androgen levels. Obese women often have high androgen levels with further elevation on ACTH stimulation. [31]
3. **SES** - More obese in high people SES (Socioeconomic status) classes and in poor countries, and obese in low SES classes and in rich countries. [31]
4. **Energy intake -** Overfeeding causes weight gain and leads to obesity. [31]
5. **Dietary fat intake** - Dietary fat is related to prevalence of overweight in ecologic studies. [31]
6. **RMR** - A low body mass and composition adjusted RMR (Resting metabolic rate) is a risk factor for weight gain, but some reports reveal that the, Overweight and obese people have higher absolute RMR. [31]
7. **Physical activity (PA) level** - A low level of PA is a risk factor for weight gain, Regular PA contributes to weight loss and weight maintenance. [31]
8. **GH level** - Low GH level is a risk factor for weight gain. [31]
9. **Insulin sensitivity -** Obese are often insulin resistant and hyperinsulinemic. [31]
10. **Skeletal muscle (SM) metabolism** - SM type I fibre type proportion is not affected by obesity, SM type IIb fibre type proportion is often elevated in obesity, SM oxidative enzyme markers are inversely related to obesity, SM LPL activity is low during obesity. [31]
11. **Smoking:** attributol is associated with a lower body weight; Cessation increases body weight in most people. [31]

EVALUATION OF OBESITY

Diet induced obesity

Obesity can be induced in rats by offering a diet containing corn oil and condensed milk special diet contains Purina Rodent Chow, corn oil and condensed milk, resulting in a composition of 14.7% protein, 44.2% carbohydrate, 15.8% lipid, 2.5% fiber, 1.2% vitamin mixture, and 19% water. Body weight and food intakes are measured, and diet replaced, every 3 to 4 days. Obesity is developed in 2–3 months. [32]

Hypothalamic obesity

Hyperphagia in rats has been reported after hypothalamic lesions. [33,34] Due to the occurrence of hypothalamic lesions, the desensitization of leptin and insulin receptor present in the hypothalamus, takes place. Moreover, it is also attributed with the over expression of NPY and AGRP resulting excessive food intake and obesity. [28]

High Fat Diet

Lard or saturated oil added to diet takes 8 weeks to develop obesity most Commonly Used model HFD contains (32.6% Protein, 33% Fat, 30% Carbohydrate, Normal chow, Lard, Casein, cholesterol, Vitamins, minerals, Yeast powder, Methionine, Nacl). [35] The induction with HFD treatment causes increased free fatty acid, LDL, cholesterol, adipocyte differentiation.

Insulin-like growth factors (IGFs) in relation to abnormal conditions

Insulin-like growth factors (IGFs) are proteins with multiple functions including stimulation of cell proliferation, inhibition of apoptosis, and enhancement of cell motility as well as the regulation of cell differentiation and transformation

(Delafontaine et al., 2004). Among IGFs, circulating IGF-1, which is mainly synthesized in the liver in response to stimulation by growth hormone (GH) through its receptor (GHR), mediates many of the pro-growth effects of GH. In the bloodstream, the majority of the IGF-1 is found in a binary complex with IGFBP (mainly IGFBP-3) proteins or a ternary complex including also the glycoprotein Acid Labile Subunit **(Juul et al., 1995)**. IGF-1R belongs to the tyrosine kinase receptor family and triggers a signal transduction cascade involving PI3K, AKT, and TOR **(Delafontaine et al., 2004)**.

A series of studies have shown that high levels of IGF-1 are associated with an increased risk of tumors including prostate, pre- and postmenopausal breast, lung, thyroid, and colorectal cancers **(Ma et al., 1999; Renehan et al., 2004; Shi et al., 2001)**. An increase in serum IGF-1 level of 100 ng/ml was shown to correspond to a 69% increase in colorectal cancer risk **(Ma et al., 1999)**. High levels of IGF-1 were also shown to be associated with a 49% increase in prostate cancer, 65% increase in breast cancer **(Renehan et al., 2004)**, and a 106% increase in lung cancer risk **(Yu et al., 1999)**. Furthermore, in worms, flies, and mice insulin/IGF-1 signaling reduces lifespan and healthspan **(Bartke et al., 2013; Fontana et al., 2010); Kenyon, 2010; Podshivalova et al., 2017)**. On the contrary, several studies have found a connection between low levels of IGF-1 and conditions such as cardiovascular diseases (CVD), diabetes mellitus, osteoporosis, and sarcopenia **(Garnero et al., 2000; Higashi et al., 2010).**

Among studies focused on the relationship between IGF-1 levels and mortality, some reported no relationship (Brugts et al., 2008); Hu et al., 2009), whereas others showed a positive association between high levels of IGF-1 and mortality **(Andreassen et al., 2009; Colombo et al., 2017; Duggan et al., 2013)** and four indicated that low levels of IGF-1 are associated with higher mortality **(Cappola et al., 2003; Friedrich et al., 2009 (Jia et al., 2014 (Miyake et al., 2016)**. Interestingly, a meta-analysis carried out by Burgers et al. in 2011 had suggested

a U-shaped relation between circulating IGF-1 and mortality **(Burgers et al., 2011)**

Because serum IGF-1 level measurements are common in the clinic, to address these controversial findings and identify an IGF-1 range consistently associated with lower mortality, we conducted a dose–response meta-analysis of prospective cohort studies assessing the relationship between IGF-1 levels and all-cause mortality. The third national health and nutrition examination survey data were instead used to identify nutrients whose intake affects IGF-1 levels.

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].

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].

MATERIALS AND METHODS

STUDY DESIGN

Patients: The number of patients was 102, divided to two groups, control group (n=50) and obese group (n=52). The study was carried out at General hospitals in Babel province, Iraq. Sample size was taken by consecutive manner.

Confirmation of Obesity: According to the level of BMI> 30 (WHO Definition).

Exclusion criteria: Eligible patients should not document with known DM, chronic liver diseases, kidney diseases, thyroid diseases, or using any medications that effect 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.

Results

Discussion

Obesity is a pathological condition with excess body fat. It is a chronic disorder with complex interactions between genetic and environmental factors. It is being characterized by high cholesterol, fatty acid levels, Insulin desensitization; high blood pressure; and excessive adipose mass accumulation. Currently, more than 1 billion adults are overweight and at least 300 million of them are clinically obese. It is defined by body mass index and further evaluated by both percentage body fat and total body fat. Obesity is a risk to many secondary conditions like cardiovascular disorder, insulin pathological resistance, retinopathy, neuropathy and cancer. Various factors modulating the development of obesity are age, sex, smoking, growth hormone level, and skeletal muscle metabolism. Experimental models used to evaluate obesity are high fat diet, high cafeteria diet, hypothalamic lesions, and monosodium glutamate induced obesity. Non-human primates, Spontaneous obese rats, Obesity due to natural allele defects in mice, V-Genetic variants in the human Uncoupled Protein-1 gene and Viral induce obesity are also preferred.

CONCLUSION:

The review may conclude that the obesity is a multifactorial disease and it is characterized by extra fat accumulation, increased BMI. It is occurred due to imbalance in energy expenditure and food intake. The assessment can be done using fat diet, genetic and viral induced obesity models. Hence the evaluation and search of new therapeutic strategies are demanded to prevent this world wide co-morbidity.

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