Detection of Insulin Resistance in Obese young men and its association with metabolic abnormalities in Najran, Saudi Arabia

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Abstract: The association between obesity and type 2 diabetes mellitus (T2DM) has been recognized for decades. The major basis for this link is the ability of obesity to engender insulin resistance (IR). Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) is an indirect marker of IR. The present study evaluated the usefulness of HOMA-IR in the prediction of the risk of the development of T2DM among overweight and obese individuals in Najran, Saudi Arabia. This study was carried out on 116 male individuals divided into 3 groups. Of these, 20 healthy control (GI), 44 prediabetic overweight and obese individuals with high normal serum glucose levels (GII) and 52 diabetic overweight and obese individuals with high serum glucose levels (GIII). Body mass index (BMI) was calculated for all individuals. In addition, fasting serum glucose and insulin levels, lipid profile and liver and kidney function tests were estimated for all individuals. The mean BMI was 21.84±1.28 kg/m^2 in GI, 28.68±2.42 kg/m^2 in GII and 33.82±2.78 kg/m^2 in GIII. The mean fasting serum glucose was 128.29±27.92 mg/dl in GII and 159.46±44.86 mg/dl in GIII. Such findings were correlated with increased fasting serum insulin levels (21.57±2.58 µU/ml in GII and 37.28±6.15 µU/ml in GIII) compared to GI (16.22±6.23 µU/ml). The mean HOMA-IR was 5.77±1.71 in GII and 12.67±4.07 in GIII compared to GI (4.07±1.04). We conclude that, increased BMI was associated with increased incidence of Insulin Resistance, dyslipidaemia and hyperuricaemia among overweight and obese individuals in Najran, Saudi Arabia..

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1. Introduction

Overweight and obesity have become a critical health problem in the world and they are considered the fifth leading risk for global deaths ***(WHO, 2012)***. At least 2.8 million individuals die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden is attributable to overweight and obesity. Obesity is a multifactorial disease with genetic, endocrinal and environmental origins, resulting from an imbalance between energy intake and expenditure, ***(Daghestani et al., 2007)***. Evidence from many Saudi national cross-sectional studies showed that there were progressive increases in body mass index (BMI) of Saudi population indicating that obesity is a crisis in Saudi Arabia ***(El-Mouzan et al., 2010)***. Obesity constitutes about 35.5% of Saudi adult population ***(Al-Nozha et al., 2005; Al-Othaimeen et al., 2007)***. Body mass index is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. The BMI is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). The BMI provides the most useful population-level measure of overweight and obesity as it is the same for both sexes and for all ages of adults ***(Stein and Colditz, 2004; US Preventive Services Task Force, 2004)***.

Insulin is the major anabolic hormone whose action is essential for appropriate tissue development, growth, and maintenance of glucose homeostasis. Insulin is secreted by the pancreatic β-cells in response to increased circulating levels of glucose and amino acids after a meal ***(DeFronzo, 1988; Shulman, 2000)***. Diabetes mellitus is the most common chronic endocrine disorder, affecting an estimated 5-10% of the adult population in industrialized Western countries, Asia, Africa, Central America and South America, and it has a large impact on society ***(Wild et al., 2004)***. Type 2 diabetes mellitus (T2DM) is a multistage process that begins as insulin resistance (IR), characterized by inability of the body to use its own insulin properly, and ends with exhaustion of the insulin-producing pancreatic β-cells, thereby leading to hyperglycaemia ***(Alqurashi et al., 2011)***. IR is measured by HOMA-IR (Homeostasis Model Assessment-Insulin Resistance) which is an indirect marker of IR. HOMA-IR was calculated, according to ***Anderson et al., (1995) and Haffner et al., (1997)***. Obesity is considered the most important risk factor for the development of T2DM , as obese individuals are seven times more likely to develop T2DM than are normal weight individuals ***(Bloomgarden, 2000)***. Evidence from epidemiologic and metabolic studies

has shown that adverse metabolic consequences of excess fat are more closely related to the location of fat than to the amount of fat ***(Despres et al., 2001; Pi-Sunyer, 2004)***. Indeed, central accumulation of fat may be a better predictor of increased risk for T2DM than is absolute fat mass ***(Kissebah, 1989)***. In addition, central obesity is strongly correlated with IR in type2 diabetic patients ***(Duman et al., 2003)***. Other factors are implicated in the development of T2DM, including family history, physical inactivity and inherited factors. ***Alqurashi et al. (2011)*** reported that many epidemiological studies of the prevalence of diabetes in Saudi Arabia, 1982-2009 showed a further increase in the prevalence of diabetes mellitus in comparison with previous studies carried out in Saudi Arabia. In this article, the principal objective was to evaluate the relationship between increased BMI and the development of IR as risk factors for T2DM among overweight and obese individuals in Najran, Saudi Arabia.

2.Materials and Methods

One hundred and sixteen male individuals overweight and obese Saudi men in Najran area (age 18—30 years, BMI ≥26 kg/m^2), were included in this study. ***The WHO (2004)*** regards a BMI greater than 25 kg/m^2 is considered overweight and above 30 kg/m^2 is considered obese. They were contacted by telephone and invited to join the study. All subjects were apparently healthy; none was taking any medication or had any medical condition known to influence body composition, insulin secretion or action. This study was approved by the Ethics of Najran community and all subjects were informed about the aim of the study.

Blood samples

Study participants were assessed in the morning after an overnight fasting (12 hours). Blood samples were collected from 116 male individuals. Of these, 44 prediabetic overweight and obese individuals (GII), 52 diabetic overweight and obese individuals (GIII) and 20 healthy control individuals (GI).

BMI and IR Calculations

BMI was calculated by the body weight in kilograms divided by the square of the height in meters. Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) is an indirect marker of insulin resistance. HOMA-IR was calculated according to ***Matthews et al., (1985)***, using the Formula HOMA-IR = [Fasting insulin (μU/ml) ‑ fasting glucose (mmol/L)/22.5].

Biochemical measurements

Insulin was estimated by Access 2 machine (BECKMAN COULTER, INC) by using direct chemiluminescent technology. Total cholesterol, glucose, high density lipoprotein (HDL), low density lipoprotein (LDL) and triglycerides (TG) were measured using COBAS INTEGRA automatic analysers (Roche Diagnostics GmbH, USA). Kidney functions, including creatinine (Crea) and Uric acid (UA), and liver functions including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TB), albumin (ALB), total protein (TP) were measured using the same method.

Statistical analysis:

All statistical analyses were performed using GraphPad InStat 3 (GraphPad Software, Inc.2236 Avenida de la Playa La Jolla, CA 92037 USA). We used a two-tailed test, and a value of $P<0.05$ was considered to be statistically significant.

3.Results

Mean age and BMI among studied groups:

The mean age of the subjects included in the study was 25.56±6.25 years in GI, 27.32±3.45 years in GII and 27.85±4.15 years in GIII. There were non-significant statistical differences in the age between groups. An extremely significant difference was observed in the mean BMI, between the tested groups (28.68±2.42 kg/m^2 in GII and 33.82±2.78 kg/m^2 in GIII) and the control group (21.84±1.28 kg/m^2), all values were highly increased in GII and GIII compared to GI, **(Table 1)**.

Effect of increased BMI on fasting serum glucose and insulin levels:

We found that, there were high increases in the fasting serum glucose level in the tested groups (128.29±27.92 mg/dl in GII and 159.46±44.86 mg/dl in GIII) compared to GI (91.56±15.86 mg/dl) and the differences were extremely significant in GII and GIII compared to GI. At the same time, the fasting serum glucose level showed extremely significant increase in GIII compared to GII, **(Table 1)**.

Such findings were correlated with fasting serum insulin levels that showed extremely significant increases between the tested groups (21.57±2.58 μU/ml in GII and 37.28±6.15 μU/ml in GIII) compared to GI (16.22±6.23 μU/ml). At the same time, these results were reflected on the ratio of the IR that showed extremely significant increases between the tested groups (5.77±1.71 in GII and 12.67±4.07 in GIII) compared to GI (4.07±1.04), **(Table 1)**.

Effect of increased BMI on lipid profile:

The present study investigated the effect of the increased BMI on lipid profile. We found extremely significant increases in the serum cholesterol levels between the tested groups (243.93±40.69 mg/dl) in GII and (294.29±42.36 mg/dl in GIII) compared to GI (195.2±15.49 mg/dl).

At the same time, there was an extremely significant increase in the serum cholesterol levels in GIII compared to GII. While, serum HDL level showed a non-significant decrease in GII (32.63±9.94 mg/dl) compared to GI (35.89±5.56 mg/dl. While, there was a very significant decrease in the serum HDL levels in GIII (28.5±10.53 mg/dl) compared to GI. On the other hand, there was a significant decrease in the serum HDL levels in GIII compared to GII. Regarding to the serum LDL level, the present study demonstrated that there were high increases in the serum LDL level in GII (172.15±40.11 mg/dl) and GIII (226.1±42.95 mg/dl) compared to GI (127.33±18.67 mg/dl), such differences were extremely significant in GII and GIII compared to GI. At the same time there was an extremely significant increase in serum LDL level in GIII compared to GII. Concerning to the serum TG level, the present study demonstrated that there were high increases in the serum TG levels in GII (195.79±27.12 mg/dl) and GIII (198.92±50.1 mg/dl) compared to GI (159.4±30.93 mg/dl), such differences were extremely significant in GII and very significant in GIII compared to the control group. While, such differences were non-significant when we compared GIII with GII, **(Table 1)**.

Effect of increased BMI on liver function tests:

The present study investigated the effect of the increased BMI on liver function tests. We found that increased BMI modified liver function tests. Such modifications were obvious in serum ALT and ALP levels. The present study demonstrated that there were high increases in the serum ALT level in GII (28.78±12.95 U/L) and (33.48±11.61 U/L) in GIII compared to GI (18.42±4.63 U/L). Such differences were non-significant in GIII compared to GII. Regarding to the serum ALP level, the present study demonstrated that there were extremely significant increases in the serum ALP level in the tested groups (73.57±14.81 U/L) in GII and (82.55±24.63 U/L) in GIII compared to GI (56.02±12.93 U/L). While, there was a significant increase in serum ALP level in GIII compared to GII, **(Table 2)**.

Effect of increased BMI on kidney function tests:

The present study investigated the effect of the increased BMI on kidney function tests. Our results showed that there was a very significant increase in GIII (0.56±0.39 mg/dl) compared to GI (0.39±0.18 mg/dl). While, this increase was non-significant in GII (0.53±0.34 mg/dl) compared to GI. At the same time, there was an obvious hyperuricaemia in GII (6.1±1.59 mg/dl) and GIII (6.28±1.88 mg/dl) compared to GI (4.9±1.64 mg/dl). While, there was a non-significant increase in serum uric acid level in GIII compared to GII, **(Table 2)**.

(Table 1): BMI, Glucose, Insulin Resistance and Lipid profile in healthy control (GI), Prediabetic overweight and obese individuals (GII) and Diabetic overweight and obese individuals **(GIII)**

		BMI (kg/m^2)	Glucose mmol/L	Insulin µU/ml	Insulin Resistance (HOMA-IR)	Lipid profile			
						Chol mmol/L	HDL mmol/L	LDL mmol/L	TG mmol/L
GI (n=20)	Mean ± S.D.	21.84 ± 1.28	5.47 ± 0.88	16.22 ± 6.23	4.07 ± 1.04	195.2 ± 15.49	35.89 ± 5.56	127.33 ± 18.67	159.4 ± 30.93
GII (n=44)	Mean ± S.D.	28.68 ± 2.42	6.01 ± 0.44	21.57 ± 2.58	5.77 ± 1.71	243.93 ± 40.69	32.63 ± 9.94	172.15 ± 40.11	195.79 ± 27.12
	P1	<0.0001***	0.002**	<0.0001***	<0.0001***	<0.0001***	0.35	<0.0001***	<0.0001***
GIII (n=52)	Mean ± S.D.	33.82 ± 2.78	10.85 ± 3.6	37.28 ± 6.15	18.67 ± 9.07	294.29 ± 42.36	28.5 ± 10.53	226.1 ± 42.95	198.92 ± 50.1
	P1	<0.0001***	<0.0001***	<0.0001***	<0.0001***	<0.0001***	0.004**	<0.0001***	0.002**
	P2	<0.0001***	<0.0001***	<0.0001***	<0.0001***	<0.0001***	0.02*	<0.0001***	0.71

P1: Compared to healthy control (GI) *P2*: Compared to Prediabetic overweight and obese individuals (GII)

(Table 2): Liver and Kidney function tests in healthy control (GI), Prediabetic overweight and obese individuals (GII) and Diabetic overweight and obese individuals **(GIII)**

		Liver function tests						Kidney function tests	
		ALT U/L	AST U/L	ALP U/L	ALB g/L	TP g/L	T.Bil mmol/L	Crea mg/dl	UA mg/dl
GI (n=20)	Mean ± S.D.	18.42 ± 4.63	18.65 ± 5.25	56.02 ± 12.93	42.03 ± 2.38	62.3 ± 3.69	4.99 ± 1.44	0.39 ± 0.18	4.9 ± 1.64
GII (n=44)	Mean ± S.D.	28.78 ± 12.95	20.69 ± 4.19	73.57 ± 14.81	41.05 ± 4.36	62.16 ± 3.99	5.13 ± 2.51	0.53 ± 0.34	6.1 ± 1.59
	P1	0.04*	0.1	<0.0001***	0.35	0.89	0.82	0.09	0.007**
GIII (n=52)	Mean ± S.D.	33.48 ± 11.61	22.07 ± 7.34	82.55 ± 24.63	40.51 ± 3.18	61.42 ± 3.35	5.27 ± 2.33	0.59 ± 0.27	6.28 ± 1.88
	P1	<0.0001***	0.06	<0.0001***	0.06	0.34	0.62	0.003**	0.005**
	P2	0.06	0.27	0.04*	0.49	0.33	0.78	0.34	0.62

P1: Compared to healthy control (GI) *P2*: Compared to Prediabetic overweight and obese individuals (GII)

4. Discussion

Our study demonstrated that, fasting serum glucose and insulin levels in over weight and obese individuals were highly increased. Such results were reflected on increasing ratio of the HOMA-IR which was strongly correlated with both fasting serum glucose and insulin levels.

In the present study, there were a significant increase in the mean BMI between the prediabetic overweight and obese individuals (GII) and the overweight and obese individuals (GIII) groups compared to the control group (GI) (*P<0.0001*), **(Table 1)**. Obesity is considered as a big problem in the Kingdom of Saudi Arabia (KSA), ***(Mahfouz et al., 2007 and Amin et al., 2008).*** ***Al-Nozha et al., (2005)*** reported that about 72.5% of Saudis are either overweight or obese. Many studies have already demonstrated that lifestyle is strongly associated with the development of overweight and obesity ***(Wahl, 1999; Yannakoulia et al., 2004 and Mahan et al., 2004)***. Obvious changes in the dietary habits in the KSA, mainly increasing the consumption of animal products and refined foods, were observed ***(Mahfouz et al., 2007 and Amin et al., 2008)***. These were accused for increasing the prevalence of both overweight and obesity observed among Saudi population in the last few decades ***(Al-Hazzaa et al., 2007)***.

The present study revealed that, there were high increases in the fasting serum glucose levels in GII and GIII compared to healthy control group (GI) (*P<0.0001*). Such results were accompanied with significant increases in the fasting serum insulin levels in GII and GIII compared to GI (*P<0.0001*). At the same time, these results were reflected on the ratio of the HOMA-IR, where HOMA-IR showed significant increases in GII and GIII compared to GI (*P<0.0001*). At the same time, HOMA-IR was found to be strongly correlated with both fasting serum glucose (r=0.97, *P<0.0001*), and serum insulin (r=0.86, *P<0.0001*). While, HOMA-IR was found to be less correlated with BMI (r=0.31, *P=0.028*). Our results are similar to findings of many other studies in which IR was found to play a major role in the development of glucose intolerance and T2DM in overweight and obese individuals, ***(Katz et al., 2000; McAuley et al., 2001; Cummings and Schwartz 2003; Sesti, 2006 and Bhatnagar et al., 2010)***. ***Bloomgarden, (2000)*** reported that obesity is considered the most important risk factor for T2DM, as obese individuals are seven times more likely to develop T2DM than are normal weight individuals. Regarding to the pathogenesis of T2DM, ***Mlinar et al., (2007)*** supposed that excess abdominal adipose tissue has been shown to release increased amounts of free fatty acids which directly affect insulin signalling, diminish glucose uptake in muscle, drive exaggerated TG synthesis and induce gluconeogenesis in the liver.

Our results revealed that abnormal lipid profile have been associated with increased BMI especially in GIII compared to GI. Such dyslipidaemia was in the form of elevated serum levels of cholesterol, LDL and TG especially in GIII . While, serum HDL showed decreased levels in the tested groups especially in GIII compared to GI (*P=0.004*), **(Table 1)**. At the same time, HOMA-IR was found to be non-correlated with serum levels of cholesterol, LDL, TG or HDL. Our results agree with many other studies that reported that people who are obese and IR often suffers from dyslipidaemia that is characterized by elevated blood TG and low HDL, ***(Sesti, 2006 and Wood, 2006)***. Also it was found that, a common underlying problem in development of IR is the body's excessive burden of fatty acids,

many of which build up in the liver as TG, ***(Savage et al., 2007)***.

The present study revealed that, increased BMI resulted in high increases in the serum ALT and ALP levels in GII and GIII compared to GI (*P=0.04 and P<0.0001,* respectively). Such increases were more obvious in GIII, **(Table 2)**. These findings agreed with a large body of evidence that showed a significant association between ALT activity and T2DM in different populations ***(Hanley et al., 2004 and Gautier et al., 2010)***. ***Bonnet et al., (2011)*** reported that ALT activity was strongly associated with both peripheral and hepatic IR and reduced hepatic insulin extraction in healthy individuals. Moreover, many studies reported that liver enzyme ALT could reflect peripheral IR incident and predict T2DM ***(Lee et al., 2004; Hanley, et al., 2004;Nakanishi et al., 2004, Wannamethee et al., 2005 and André et al., 2007)***. However, the physiopathological mechanisms that underlie the association between ALT, and the risk of diabetes remain poorly understood, ***(Hanley, et al., 2007)***.

In the present study, there was an obvious hyperuricaemia in GII and GIII compared to GI (*P=0.007and 0.005,* respectively). While, there was a non-significant increase in serum uric acid level in GIII compared to of GII. Our results are similar to the findings of many authors who stated that IR is commonly associated with hyperuricaemia, ***(Srinivasan et al., 2002; Moreno et al., 2002 and Weiss et al., 2004)***. Moreover, abdominal obesity was found to be commonly associated with increased serum uric acid concentration, ***(Ishizaka et al., 2005; Oh et al., 2006; Lin et al., 2006; Kim et al., 2007; Lim et al., 2010 and Civantos Modino, 2012)***. It was found that elevated fasting blood glucose may be a prerequisite for hyperuricaemia in susceptible individuals who develop abdominal fatness. It is conceivable that uric acid, along with lactic acid and redox status, is a determinant of gluconeogenesis. Alternatively, with increased keto acid formation overnight, in those who are abdominal fat, uric acid will rise because of competition between acids for renal excretion, ***(Fam, 2002 and Cahill, 2006)***.

Conclusions:

We conclude that, increased BMI was associated to increased IR, T2DM, dyslipidaemia and hyperuricaemia. Reduction in overweight and obesity rates are of considerable importance to public health. Therefore, we recommend a national obesity prevention and management program at community level for weight management through the promotion of a healthy lifestyle, family educational seminars and the reinforcement of indoor exercises.

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