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Original Research Article

Relationship between body mass index, liver enzymes and high-sensitivity C-reactive protein in type 2 diabetes mellitus patients

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ABSTRACT

Background: Obesity is a frequent co-morbid condition associated with excessive increase in weight. It is one of the most important modifiable risk factors in the pathogenesis of type 2 diabetes mellitus (T2DM). Obesity may be associated with liver disease and the progression of hepatic dysfunction. Also, highly sensitive C-reactive protein (hsCRP), which is elevated in inflammatory situations, can be produced by monocyte-derived macrophages in adipose tissue may also disrupt liver functions.
Methods: A case control study with 50 patients of T2DM and 50 age and sex matched individuals were taken to serve as controls.
Results: The body mass index (BMI) and waist circumference were increased in T2DM patients as compared to controls. However, the variations in liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum alkaline phosphatase (ALP) and hsCRP were increased in individuals of normal BMI as compared with individuals of overweight BMI.
Conclusions: Individuals with normal Body mass index had an increased risk of developing T2DM along with progression of hepatic dysfunction. No associations were observed between chronic low-grade inflammation and BMI and with pathogenesis of obesity-related insulin resistance.

Keywords: ALP, Glycosylated hemoglobin, hsCRP, ALT, AST

INTRODUCTION

Obesity is the leading public health challenge in India and across the world. Indians are highly susceptible to diabetes with modest overweight, central obesity, and decrease in physical activity. Obesity is a frequent co-morbid condition associated with excessive increase in weight.[1]

The incidence and prevalence of diabetes mellitus (DM) and cardiovascular disease in India is increasing and is a result of dietary habits and lifestyle.[2] National surveys showed that there has been a marked decrease in under nutrition and significant increase in the prevalence of overweight and obesity, more specifically among the urban populations of India.[3] DM and obesity share many common risk factors. Previous research has established that obesity is associated with insulin resistance and decreased insulin sensitivity in the aged population with newly diagnosed type 2 DM and a predictor of incident type 2 DM.[4] A healthy body mass index (BMI) is believed to be helpful to reduce the prevalence of DM in adults. A World Health Organization (WHO) panel reported that there is increasing evidence of a high prevalence of type 2 DM as well as cardiovascular disease among Asian population at a lower BMI than the standard cut-off of 25.0 kg/m^2.[5]

An increase in blood glucose level will result in increase in BMI causing increased lipid biosynthesis and hence body weight. Insulin act through specific cell receptor

which results in enhanced glucose uptake into the cell. As BMI increases, insulin resistance also increases which results in increased blood glucose level in body. Since body weight is associated with BMI, it may be expected that BMI should correlate with blood glucose levels.[6] Obesity is known to induce insulin resistance due to decrease in insulin-sensitive receptors as the weight increases.[7] It is therefore, expected that BMI should correlate with blood glucose levels.[6,7] Increase in blood glucose level have associated with increase in lipid biosynthesis (lipogenesis) and hence, an increase in weight.[8,9]

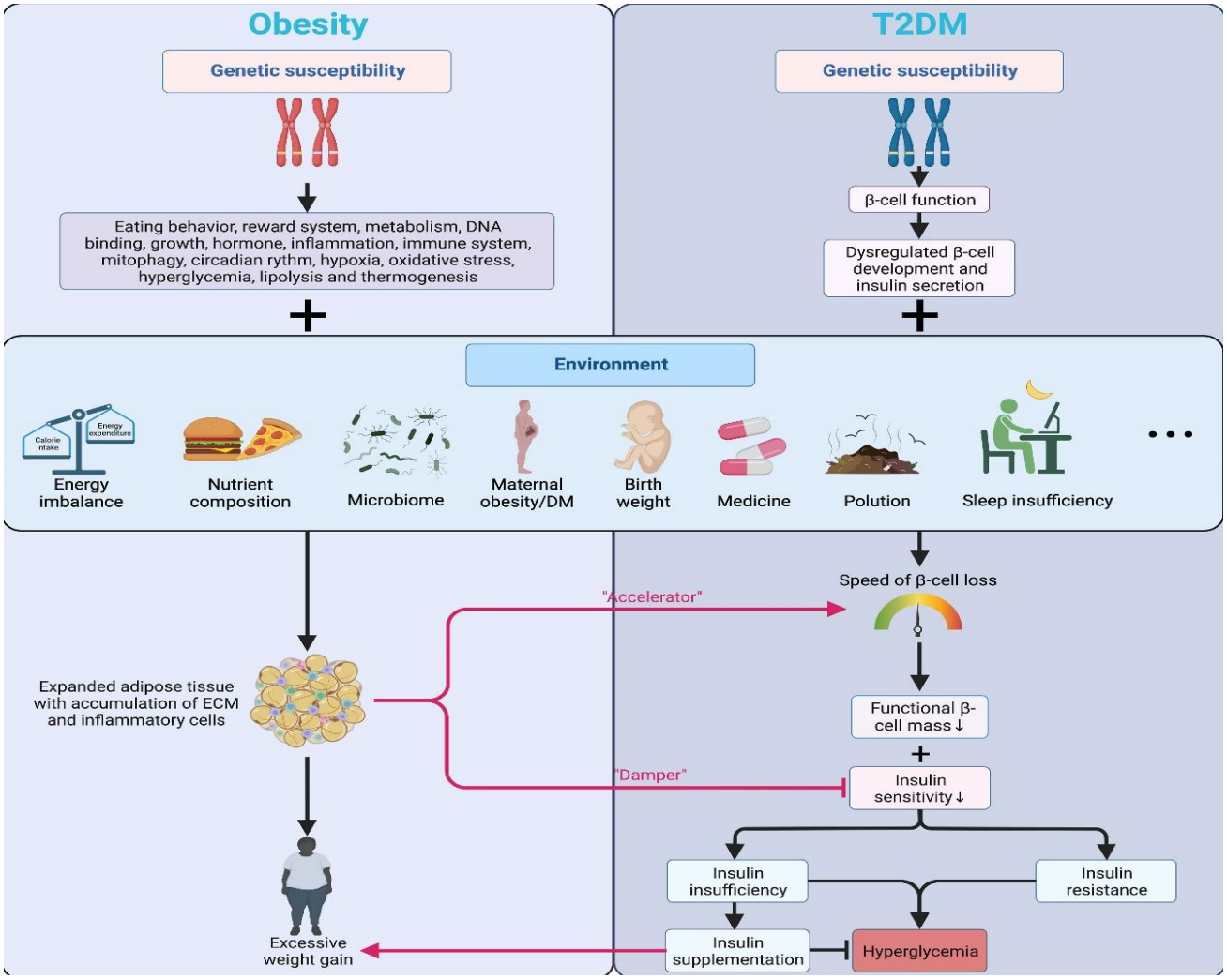

Figure 1: Genetic and environmental factors affecting islet function and connecting obesity and T2DM. Genetic factors mainly alter the energy balance in obesity while regulating the development and function of b-cells in T2DM. Being further promoted by various environmental factors, obesity accelerates the b-cell loss and blunts insulin signaling in T2DM. Meanwhile, insulin prescribed to patients with T2DM can have a weight-increasing effect.[6]

The BMI captures the degree of overweight and obesity; it ignores body fat distribution. Visceral fat tissue is metabolically more active than non-visceral fat and secretes more hormones and cytokines, which may be important for the development of diabetes mellitus. Measuring waist circumference is a simple means of assessing the levels of visceral fat. Increased waist circumference is also closely associated with an increased risk of diabetes.[8] As overweight and obesity are among the strongest known risk factors for type 2 diabetes, risk statements based on anthropometric measurements should be as precise as possible and allow for the complex interactions between these parameters.[6,8]

Systemic inflammation could be the causative link between obesity, diabetes, and cardiovascular diseases, as it induces inflammatory processes in the vessel wall. The chronic inflammatory response increases the production of markers of inflammation i.e., C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α).[9,10] Elevated concentrations of hsCRP were seen when obesity and diabetes were studied separately.

Obesity is a well-known contributor to insulin resistance; we further evaluated the relationship of insulin resistance and weight status on the risk of elevated liver enzyme levels. Obesity may be associated with liver disease and progression of hepatic dysfunction, and obesity may impair liver function by a variety of mechanisms.[11] Overweight or obese individuals have higher risk of developing steatosis, causing abnormal liver function. In individuals with obesity, high levels of cytokines including interleukin-6 (IL-6) and C-reactive protein (CRP) may disrupt liver functions such as production of hepcidin which can lead to hepcidin-related iron deficiency anaemia and may lead to some types of liver diseases such as NAFLD and liver cancer.[10]

The serum levels of four enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and γ-glutamyl transferase (GGT) are generally used in assessing liver functions. ALT and AST are found mostly in the liver, and serum levels of AST and ALT are considered as specific markers for hepatic dysfunction. ALP is an enzyme that is primarily present in the liver, bones, intestine, and kidneys. The higher serum levels of ALT, AST, ALP and GGT are reported in several diseases and increased levels of these enzymes are frequently reported in people with obesity.[12] The association between obesity and serum biomarkers of liver function, independent of dietary intake and physical activity, is not yet clear.

Due to the role of liver enzymes in the body's metabolism, if the link between obesity and serum levels of liver enzymes is proven, this finding may be a clue as a possible mechanism by which obesity plays a role in the risk of a broad range of diseases such as fatty liver, diabetes, and cancers.

Objective

The aim of the study was to examine the relationship between BMI, liver enzymes (ALT, AST, and ALP) and hsCRP levels in T2DM patients.

METHODS

This was a case control study comprising of 100 individuals. The study group included 50 patients above the age of 30 years with clinically diagnosed type 2 diabetes mellitus who were either visiting out-patient department or admitted in the department of medicine, Guru Nanak Dev Hospital attached to Government Medical College, Amritsar from November 2021 to December 2022.

Inclusion criteria

The subjects selected for the study were grouped as follows: group 1-50 clinically diagnosed cases of type 2 diabetes mellitus patients above the age of 30 years, and group 2-50 healthy asymptomatic individuals as controls.

Exclusion criteria

Patients with type 1 diabetes mellitus, chronic liver diseases (bronchiectasis and pulmonary fibrosis), chronic renal diseases and are receiving dialysis, thyroid disorders or any chronic infections like tuberculosis are excluded from the study. Also, smokers and individuals with high (>120 g/l) alcohol consumption were also excluded.

All the subjects included in the study were investigated for: fasting blood glucose levels were estimated by GOD-POD method, glycated hemoglobin (HbA1c) levels were measured by ion-exchange resin method, liver enzymes (ALT, AST, and ALP) were estimated by using IFCC method and hsCRP is measured by turbidimetric immunoassay.[13-18]

Statistical analysis

Mean±SD was calculated for all the parameters analyzed and were compared by student 't' test and analysis of variance (ANOVA) (SPSS version 17) for correlation amongst different parameters. P value considered: p value <0.05 – significant, and p value <0.001 – highly significant.

RESULTS

The study consists of 50 T2DM patients which includes 14 males and 36 females. Similarly, the control group comprises of 50 healthy individuals of which 19 were males and 31 were females. The age of T2DM patients ranges from 30 to 80 years with a mean of 59.26±6.40 years. Also, the age of healthy individuals ranges from 30 to 80 years with a mean of 45.68±11.12 years (Table 1).

Table 1: Segregation of T2DM patients and controls on the basis of age and sex.

Age (years)	T2DM patients		Controls	
	Males	Females	Males	Females
30-45	1	4	9	24
46-60	8	24	9	3
>60	5	8	1	4

Baseline characteristics between T2DM patients and controls are given in Table 2 which further depicts the mean values of age (years), height (cm) and weight (kg).

Table 2: Comparison of baseline characteristics between T2DM patients and controls.

Baseline parameter	T2DM patients Mean±SD	Controls Mean±SD	P value
Age	59.26±6.40	45.68±11.12	0.02
Height (cm)	169.6±8.47	175.4±9.2	>0.05
Weight (kg)	74.48±8.10	70.96±7.2	>0.05

The BMI were studied in subjects i.e., in T2DM patients and in controls. The mean levels were 25.99±2.12 kg/m^2 and 23.77±2.38 kg/m^2 in T2DM patients and controls respectively. A significant increase (p≤0.05) in BMI was observed in T2DM patients as compared to controls (Table 3).

Table 3: Comparison of body mass index (kg/m^2) in type 2 diabetes mellitus patients and controls.

S. no.	Groups	BMI (kg/m^2)	P value
1	T2DM patients	25.99±2.12	0.01*
2	Controls	23.77±2.38	

*Statistically significant (p≤0.05)

The comparison of waist circumference in T2DM patients and controls depicts that the waist circumference was higher in T2DM patients with mean±SD of 20.43±3.88 inches as compared to controls with mean±SD of 18.83±3.99 inches (Table 4).

Table 4: Comparison of waist circumference (inches) in type 2 diabetes mellitus patients and controls.

S. no.	Groups	Waist circum-ference (inches)	P value
1	T2DM patients	20.43±3.88	0.01*
2	Controls	18.83±3.99	

*Statistically significant (p≤0.05)

The comparison between normal BMI and overweight BMI represents that serum FBG levels, HbA1c levels, Liver enzymes, and hsCRP levels were increased in T2DM patients of normal BMI as compared to overweight BMI (Table 5).

Table 5: Variations in serum fasting blood glucose levels, HbA1c levels, liver enzymes, and hsCRP levels according to body mass index in type 2 diabetes mellitus patients.

Parameters	Normal BMI (18.5-24.9)	Overweight BMI (25-29.9)	P value
Serum FBG (mg/dl)	178.3±26.85	162.8±26.0	p>0.05
HbA1c (%)	8.01±0.74	7.56±1.46	
ALT (U/l)	60.0±17.12	56.75±19.0	
AST (U/l)	59.69±16.78	57.05±17.86	
ALP (U/l)	143.0±80.4	135.5±32.8	
hsCRP (mg/dl)	6.65±1.95	6.39±2.09	

In T2DM, the level of serum fasting blood glucose and HbA1c were higher in non-veg diet with mean±SD of 173.4±27.41 mg/dl and mean±SD of 8.06±1.46% respectively as compared to veg diet. The serum ALP level was increased in T2DM patients which were on veg diet with mean±SD of 140.59±59.37 U/l and decreased in T2DM patients which were on non-veg diet. But the hsCRP level were increased in patients of T2DM which were on veg diet with mean±SD of 6.61±1.93 mg/dl and decreased in patients of T2DM which were on non-veg diet with mean±SD of 6.08±2.29 mg/dl. 28. The serum ALT level (59.46±19.20 U/l) as well as serum AST levels (58.03±17.23 U/l) were higher in T2DM patients which were on veg diet as compared to T2DM patients which were on non-veg. The serum ALT level and serum AST level in T2DM patients which were on non-veg diet were 53.64±17.38 U/l and 57.23±16.09 U/l respectively (Table 6).

Table 6: Variations in serum fasting blood glucose levels, HbA1c levels, liver enzymes and hsCRP levels in type 2 diabetes mellitus patients according to dietary habits (veg and non-veg).

T2DM patients	Veg	Non-veg	P value
Serum FBG (mg/dl)	164.43±26.24	173.4±27.41	>0.05
HbA1c (%)	7.48±1.23	8.06±1.46	>0.05
Serum ALP (U/l)	140.5±59.37	133.29±19.96	0.67
Serum ALT (U/l)	59.46±19.20	53.64±17.38	>0.05
Serum AST (U/l)	58.03±17.23	57.23±16.09	>0.05
hsCRP (mg/dl)	6.61±1.93	6.08±2.29	0.64

DISCUSSION

Obesity is the principal cause of insulin resistance shared with metabolic dysregulation as well as hypertension and abnormal lipid metabolism predisposing individuals to the development of T2DM.[8]

The ectopic expansion of adipose tissue and excessive accumulation of certain nutrients and metabolites damage the metabolic balance via insulin resistance, dysfunctional autophagy, further intensifying the dysregulation of immunometabolism through low-grade systemic inflammation, leading to an accelerated loss of functional B-cells and gradual elevation of blood glucose.[6,9] However, T2DM can also occur inversely before obesity in some individuals with inherent insulin resistance resulting in increased hepatic glucose production and elevated insulin levels, which are the actual cause of obesity. Obesity signifies excess adipose tissue. The most widely used method for screening is determination of the BMI.[19]

The present results underline the importance of BMI and waist circumference to estimate the risk of T2DM,

particularly for individuals of low or normal weight. The obesity induced transition from insulin resistance to T2DM involves dysfunction of both pancreatic α- and β-cells resulting in upregulation of hepatic gluconeogenic gene transcription with the cytokines and adipocytokines released in systemic inflammation suppressing insulin action which in turn, increases hepatic gluconeogenic enzymes transcription.

Both BMI and waist circumference serve as parameters to estimate general or abdominal fat masses, respectively. It is assumed that the abdominal fat mass is of particular importance in the development of not only type 2 diabetes, but also of other chronic diseases, including cardiovascular diseases.[8]

Comparison of BMI which shows a highly significant increase in BMI in T2DM patients as compared to controls with mean levels 25.99±2.12 kg/m^2 and 23.77±2.38 kg/m^2 in T2DM patients and controls respectively with highly significant difference ($p \leq 0.001$) (Table 3). This observation is in accordance with the U.S. Department of Health and Human Services Centres for Disease Control and Prevention (2007) which states that the risk of diabetes is 93 times greater if BMI is 35 kg/m^2 and the frequency rates of diabetes have increased in parallel with the rates of obesity. Other tools for screening obesity includes waist circumference and waist-to-hip ratio.

The guidelines of the German Obesity Society and World Health Organisation define overweight as a BMI of at least 25 kg/m^2.[20] BMI between 25 and 29.9 kg/m^2 is defined as pre-obesity; BMI of at least 30 kg/m^2 is defined as obesity. Although, the BMI includes the degree of overweight and obesity, it ignores body fat distribution which is important for development of DM. Measuring waist circumference is a simple means of assessing the levels of visceral fat. In addition, the musculature is an essential determinant of insulin resistance, therefore, at a given fat mass, individuals with low muscle mass may have a greater risk of T2DM than those with larger muscle mass.[21]

Waist circumference was higher in T2DM patients with mean±SD of 20.43±3.88 inches as compared to controls with mean±SD of 18.83±3.99 inches with highly significant difference ($p \leq 0.001$) between them (Table 4).

This is in line with the study done by Schulze et al which also states that increased waist circumference is also closely associated with an increased risk of DM.[22] However, current guideline of obesity and DM only recommend that waist circumference should be measured from BMI of 25 kg/m^2, as this is the level at which the increased risk of DM is thought to start.

BMI and waist circumference serve as parameters to estimate general or abdominal fat masses, respectively. It is assumed that the abdominal fat mass is of particular importance in the development of not only type 2 diabetes, but also of other chronic diseases, including cardiovascular diseases and some forms of cancer.[11,23] It is clear from our studies that the strength of the association of waist circumference with the risk of type 2 diabetes depends on BMI. Thus, the relationship between waist circumference and the risk of type 2 diabetes is more marked at low BMI than at higher BMI. In individuals with low BMI, waist circumference is a more exact measure of visceral fat, as these individuals mostly possess less subcutaneous fat that may affect waist circumference.

The T2DM patients were divided according to BMI (kg/m^2) into normal (18.5-24.9) and overweight (25-29.9) category in which it was observed that in normal category, all the parameters were increased as compared to overweight category but this variation did not show any significance ($p>0.05$) when compared between normal category and overweight category (Table 5).

In the present study, the T2DM patients were segregated in accordance with the dietary habits i.e., veg and non-veg. The level of FBG and HbA1c were high in T2DM patients which were non veg with mean±SD of 173.4±27.41 mg/dl and 8.06±1.46% respectively (Table 6).

But when level of serum ALP, hsCRP, serum ALT and serum AST were compared, it was found that levels of serum ALP, hsCRP, serum ALT and serum AST were increased in T2DM patients which were on veg diet with mean±SD of 140.59±59.37 U/L, 6.61±1.93 mg/dl, 59.46±19.20 U/L, and 58.03±17.23 U/L respectively. Thus, this variation was not statistically significant ($p>0.05$) (Table 6).

The variation between BMI and glycemic index (serum fasting blood glucose and HbA1c) was in line with the study done by Martina et al who discovered a substantial positive association between BMI and HbA1c.[24] Similarly, Babikr et al also discovered a linear relationship between BMI and HbA1c.[25]

Our variation in between serum ALP and BMI was in accordance with the study done by Khan et al which indicated a positive relationship for the activity of ALP enzyme with fat accumulation in adipose tissue.[26] In obesity, the activity of ALP is enhanced and anticipated disproportionate intracellular fat depots. In return, ALP is released from adipose tissue into the blood circulation in excessive amounts. Yet, no comprehensive clinical study has been conducted to find out an association of serum ALP level with obesity. Chronic low-grade inflammation and an activation of the immune system are involved in the pathogenesis of obesity-related insulin resistance and type 2 diabetes.[6] Adipose tissue, liver, muscle, and pancreas are themselves sites of inflammation in presence of obesity.[10]

Limitations

The limitations of this study include the small sample size from a single centre. Multicentre studies on larger T2DM populations are warranted to further validate the findings.

CONCLUSION

The present study revealed that exact estimation of T2DM risk requires the measurement of both BMI and waist circumference along with parameters of glycemic control (FBG and HbA1c). This is particularly important for persons of low or normal weight. Individuals with normal BMI had an increased risk of developing T2DM along with progression of hepatic dysfunction. No associations were observed between chronic low-grade inflammation and BMI and also with pathogenesis of obesity-related insulin resistance.

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