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AN ASSESSMENT OF INSULIN RESISTANCE (IR) & TUMOR NECROSIS FACTOR ALPHA (TNF-α) ASSOCIATION WITH TYPE II DIABETES MELLITUS (T2DM) CASES

Dr. Amina Iqbal, Dr. Hamd Zahra, Dr. Mahpara Asif
King Edward Medical University

Abstract:
Objective: *T2DM (Type 2 Diabetes Mellitus) and IR (Insulin Resistance) have an association with each another. Conditions of T2DM and Obesity are an inferior-status prolonged infection, which further results in increased levels of inflammatory markers like interleukins 6 (1L-6), TNF-α and C-reactive protein (CRP). The outcome of various studies is very controversial, resultantly, TNF-α association with obesity persuaded T2DM and insulin resistance is indistinguishable. Determination of the study is to make a relationship between levels of IR and TNF-α in obese and non-obese T2DM patients.*
Methods and Patients: *We completed this relative study at Allied Hospital, Faisalabad from March to October 2017. TNF-α levels and IR were governed and associated in 90 patients out of which 50 were obese and 40 were non-obese patients with a T2 diabetic. ELISA was used for determination of TNF-α and serum insulin levels and HOMA-IR was used for calculation of insulin resistance. With the help of independent sample t-test evaluation between groups also done. The considered P-value (< 0.05) was statistically significant.*
Results: *Mean TNF-α values and HOMA-IR were considerably higher in obese T2DM patients i.e. (17.13 ± 8.77) and (10.96 ± 4.69), with respect to non-obese patients of T2DM i.e. (3.40 ± 5.05) and (3.49 ± 2.36) respectively. In females, the recorded mean HOMA-IR was (12.85 ± 10.54) as compared to males (6.52 ± 7.03) (p-value 0.006).*
Conclusion: *The TNF-α part in IR, induced through obesity, is explained by increased inflammation in obese diabetics. TNF-α levels can be reduced and insulin sensitivity can improve in T2DM with reduction of weight in obese individuals.*
Keywords: *Type 2 Diabetes Mellitus (T2DM), Insulin Resistance, Tumor Necrosis Factor Alpha (TNF-α) and Obesity.*

Corresponding author:
Dr. Amina Iqbal,
King Edward Medical University

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INTRODUCTION:

In Type 2 diabetes mellitus (T2DM), blood sugar levels increment is due to defects in exudation of insulin or its action [1]. In the year 2000, the estimated dominance of the DM in the world was about 171 million people and it will be probably more than 100% increased till the year 2030 which will make this figure up to about 366 million [2, 3]. Comparatively in Pakistan in the year 2000, the prevalence of DM was around 5.2 million and probably it will reach up to 13.9 million by the year 2030 [2]. The dominance of T2 DM is about 90% of all the diabetes cases recorded between Jan-March 2018 [1].

T2DM is directly linked along with insulin hostility and mostly develops in overweight and obese people [3]. Pakistan's National Health Survey discovered that about 25% of total inhabitants are suffering due to obesity [4]. Adipose tissue, on the one side stores the surplus calories and on the other side, it vigorously conceals multiple substances like cytokines, hormones and fatty acids which can act in a secret or endocrine manner [5]. The major cause of the many metabolic disorder is obesity and it is likely to linger the infection and related to T2DM or IR [6]. TNF-α may function as vital risk element for forthcoming development of T2DM and it is available in abundance in obese persons and It can ascertain a novel mark for the satisfying envelopment [5]. TNF-α can cause insulin resistance in multiple ways as it is a pro-seditious adipokine and is release through macrophages of fatty tissue [5, 7].

After review of the previous literature, it comes to the notice that TNF-α has an association with insulin resistance like the study of Bertin et al has discovered that body mass index (BMI) is related to TNF-α but not to the level of blood glucose. A study by Bhatty et al [8, 9] revealed that TNF-α has no association with insulin resistance, BMI and abdominal circumference. In the same way, Sujata et al 2010 in their study came to know that serum TNF-α was not associated with insulin, HOMA-IR (homeostatic model assessment-insulin resistance) and with obesity parameters in local people [10]. Review of the Literature revealed that TNF-α is belonged to insulin resistance in such a way that body mass index (BMI) has an association with TNF-α, however, it did not associate to blood glucose levels (in light of the study by Bertin et al). Another study by Swaroop et al showed that tenderness plays an important part in the growth of IR in males commonly with higher BMI [11]. Study by Rajajajeswear revealed that TNF-α absorption has a solid association with BMI and increased in the obese T2DM patients [5].

Keeping in view the outcome of previously mentioned studies on the part of TNF-α and IR are greatly controversial and our understanding is not comprehensive. For provocative markers and insulin resistance in T2DM, limited studies have conducted on south Asian people particularly in Pakistan. However, an affiliation of TNF-α with obesity persuaded T2DM and IR is quite uncertain. Planning to conduct the present-day studies are to define and match the intensities of IR and TNF-α in obese and not-obese T2DM patients. The finding of the study will help to establish the part of inflammatory markers with insulin resistance in obese-mediated diabetics in Pakistani inhabitants. It will generate new data for our population directly affecting the management of patients with diabetes. Moreover, it would be helpful for the researchers to develop a way forward for controlling TNF-α and IR state. Prevention of type 2 diabetes and its related complications is the primary importance for the present period as the prevalence of T2DM is having a regular rising trend.

Purpose of the conduct of this study is to determine and equate TNF-α and IR stages in obese versus non-obese T2 diabetics.

MATERIALS AND METHODS:

We completed this relative study at Allied Hospital, Faisalabad from March to October 2017. A sample size of 90 patients assessed by means of ninety percent power of the test. Level of importance was five percent with an expected mean value of TNF-α in obese type 2 diabetic group as 215.8 and the non-obese diabetic group as 168.5 [5]. The technique used was "Non-probability convenient sampling". Cases of T2DM (registered and physician-detected) regardless of gender factor and age ranging from 30 – 75 years, presented for registration. We did not include the patients of insulin dependency, Type – I diabetics, on drugs which can decrease insulin resistance e.g. Metformin, Thiazolidinedione users for last 6 months, asthmatic patients for last 5 years (TNF-α levels are higher in lung disorders) and smokers on the basis of history as smoking effect the inflammatory pathways (taking 20 packs of citrates/year for last two years).

Pre-informed written consent secured from patients and these patients reported on the other day with an overnight fasting of 12-hour. Stadiometer for height in meters and weight machine for weight in Kg were used. The formula used for BMI calculation; weight

(kg)/height (m^2). In light of the results of BMI, these patients distributed into two groups. A cut-off value of BMI was 25kg/m^2. After 12-hour fast 5ml venous blood collected by aseptic measures for laboratory parameters like fasting insulin levels, fasting blood glucose and TNF-α. These samples than centrifuged and kept in -20^{0}C. Serum distributed into three groups (one batch for fasting insulin level, 2nd batch for TNF-α and 3rd batch for fasting blood sugar and lipid profile). HOMA method (homeostatic model assessment) was used for insulin resistance calculation, which is certified as a trusted measure of insulin sensitivity. By using enzyme amplified sensitivity immunoassay (EASIA) determination of insulin performed (INS-EASIA, catalogue no. KAP1251, DIA source Immuno Assays S.A, Belgium). The insulin levels range from 5 to 19 µ IU/ml. While TNF-α was resulted by using immune enzymatic assay.

Detectable concentration ranges from 4.6 to 12.4 pg/ml. Glucose oxidase method was used for measurement of fasting blood glucose. A special performance formulated and used for recording of all the collected information.

We collected and evaluated data on SPSS. Countable variables (age, height, weight, fasting blood glucose, TNF-α and IR) offered as mean ± S.D, whereas, qualitative variables (gender and obesity) offered as frequency and ratios. The P-value < 0.05 was marked as substantial. Independent sample t-test/Mann Whitney U-test was used between two groups comparison. Confounders, like age and gender, were precise by stratification.

RESULTS:

For study and laboratory testing, examination of 110 eligible patients was carried out from diabetic OPD of the hospital. A total of 90 active patients out of 110 eligible patients (Eight patients declined consent due to previous involvement in other research studies. Six patients failed to appear in the first visit for sample collection and 6 samples were hemolysis during sample collection, hence discarded) assessed for the clinical and laboratory outcome. Out of 90 patients, 50 (55.56%) were obese and 40 (44.44%) were non-obese, patient's age was (50.63 ± 9.89) years out of which 26 were male and 64 were female. Mean + standard deviance of TNF-α and HOMA-IR were (11.02 ± 10.03) and (7.64 ± 5.38) pg/ml, respectively.

In obese T2 diabetic patients mean fasting glucose value was higher (171.32 ± 86) with respect to non-obese patients (156.78 ± 27.16), p-value = 0.030. Moreover, mean fasting insulin in obese patients was also higher (41.55 ± 22.37) vis-a-vis non-obese patients (8.71 ± 11.49), p-value < 0.01. In the same way, mean HOMA-IR and TNF-α was also higher in obese versus non-obese patients, p-value < 0.01.

Table – I: Research Variables (Mean, SD, Range, Minimum and Maximum)

Variables	Units	Mean	S.D	Range	Minimum	Maximum
Age	Years	50.63	9.89	43	32	75
Height	m^2	1.61	0.11	0.42	1.43	1.85
Weight	kg	71.01	12.32	55	45	100
Body mass index	kg/m^2	27.45	5.19	24.97	16.14	41.11
Duration of disease	Years	3.18	1.27	5	1	5
Fasting Blood Glucose	mg/dl	164.68	31.11	180	60	240
Serum Insulin (F)	µIU/ml	26.96	24.55	109.42	1.78	111.2
HOMA-1R	-	11.02	10.03	44	0.7	44.7
TNF-$^{\alpha}$	pg/ml	7.64	5.38	21.82	0	21.82

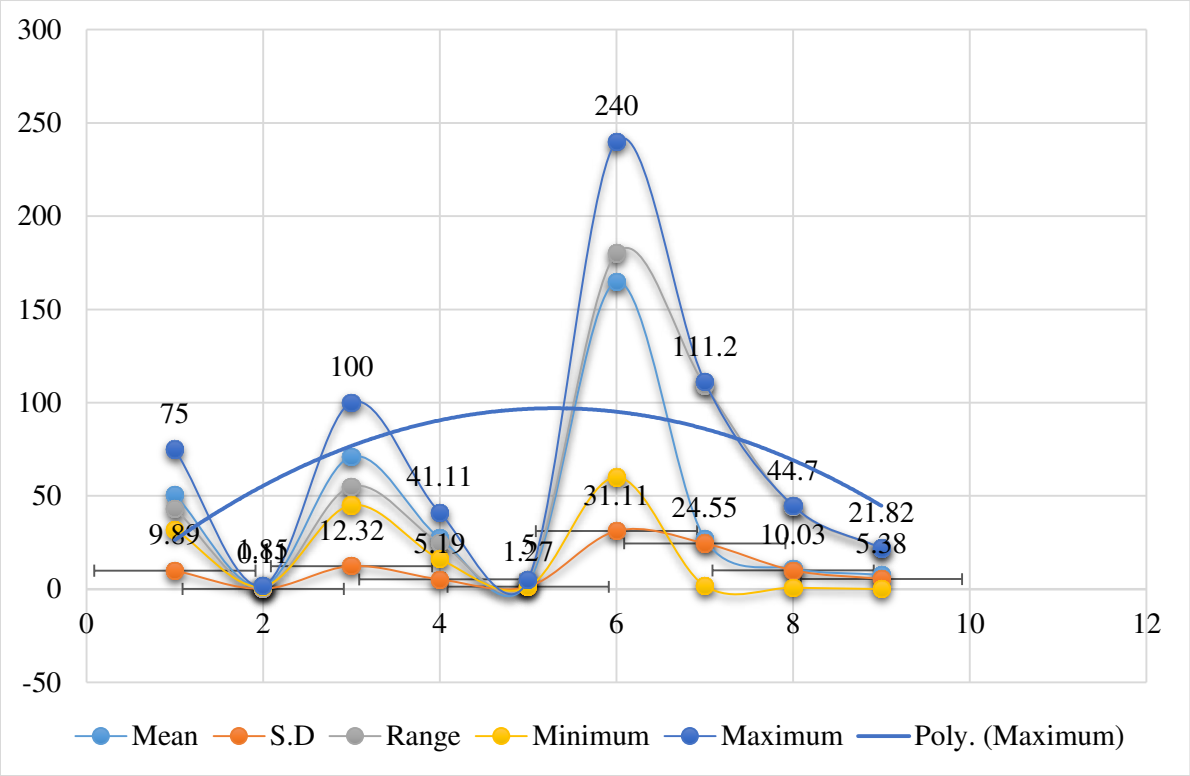
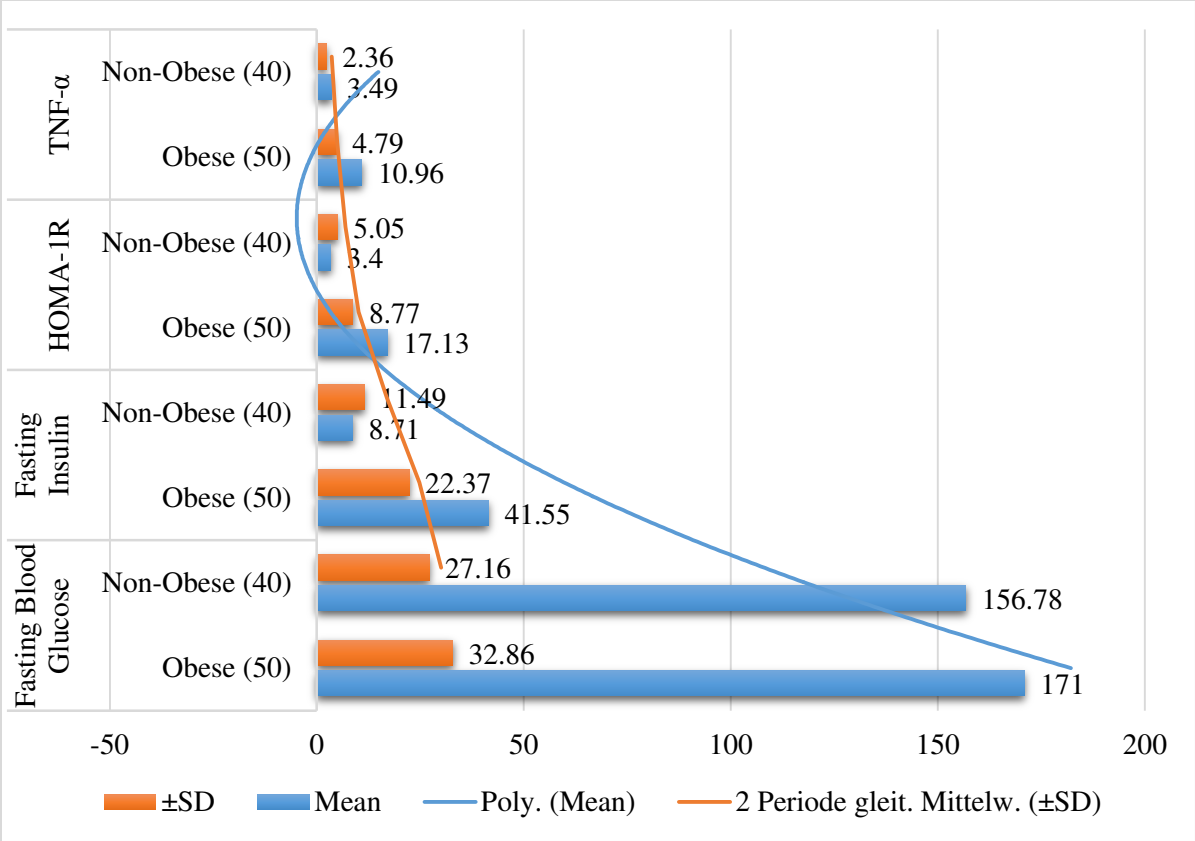


Table – II: Biochemical Parameters

Type 2 Diabetics	Units	BMI	Mean	±SD	P-Value
Fasting Blood Glucose	mg/dl	Obese (50)	171	32.86	0.03
		Non-Obese (40)	156.78	27.16	
Fasting Insulin	µIU/ml	Obese (50)	41.55	22.37	<0.01
		Non-Obese (40)	8.71	11.49	
HOMA-1R	-	Obese (50)	17.13	8.77	<0.01
		Non-Obese (40)	3.4	5.05	
TNF-$^{\alpha}$	pg/ml	Obese (50)	10.96	4.79	<0.01
		Non-Obese (40)	3.49	2.36	



DISCUSSION:

TNF-α theorized to relate obesity to IR. Sample evaluation from human and animal revealed it in adipose tissue, TNF-α expression recorded significantly higher in obesity and the same has reduced on weight reduction [12, 13]. We resolute and matched IR and TNF-α levels in obese contrasted with non-obese T2DM patients.

Higher levels of TNF-α, HOMA-IR and fasting insulin noted in obese T2DM patients as compared to non-obese and the same in several studies [5, 2, 13]. TNF-α and HOMA-IR were high in females with respect to males. The most expected cause for the increase in levels of TNF-α and HOMA-IR is because of higher BMI reported in females with respect to the male and unequal ratio of male/female in our population. In the research by Bhatty et al, higher levels of TNF-α found in males Vs females, however, HOMA-IR were more in females as compared to males. But in this study non-obese and T2 diabetics excluded and completed on the obese subject [9].

In our conclusion, TNF-α was higher in both diabetic groups, however, TNF- a was more in obese as compared to non-obese T2 diabetics. In a study conducted by Nilsson et al, same like results were attain in which levels of TNF-α were 23% higher in lean T2DM and in obese T2DM people, this increase was 51%. Katsuki et al concluded that TNF-α is increased in obese T2DM and remain the same in lean T2DM [14, 2]. As per Hotamisligil et al, a decrease in the body weight in obese people is associated with drop-in TNF-α levels and in higher insulin sensitivity. In our current conclusion it is prominently proved that in obese T2DM, TNF-α levels significantly rose up with respect to non-obese T2 diabetic [12].

Goyal R et al during his study on Indian population in 2012 found that the levels of TNF-α were very high in obese T2 diabetics as compared to our study, in which, TNF-α mean values were lower as compared to their values [15]. However, the same results, like our study, achieved in international Annals of King Edward Medical University studies done in Caucasians.

In the Pakistani population, obesity is more disposed to its fatal effects because of its higher frequency. Consideration was inefficiently in insulin therapy's effect on inflammatory markers levels among obese and non-obese diabetics. There is a requirement to

find out the outcome of insulin therapy for neutralization or reduction of TNF-α levels and further in-depth studies on the gene level are mandatory so that final inference can be established from the above observations.

An ultimate conclusion is not possible to ascertain on examining the samples of a small number of people and the limited period for observation. For a better and more informative conclusion, more observatory period and a considerable number of patients need proper assessment. Moreover, the study was only on T2 diabetics and for the conclusion the aftermath of early age seditious markers, it is necessary to make inquiries on T1 diabetes mellitus as well.

CONCLUSION:

In obese T2 diabetes cases, the levels of TNF-α are greater with respect to non-obese diabetics. TNF-α plays a vital role in IR associated with obesity and T2DM in humans and our current observations add further support to the evidence.

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