Inter-relationship of Pro- and Anti-inflammatory Biomarkers with the development of Type 2 Diabetes Mellitus

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ABSTRACT

Purpose: There has been growing evidence that inflammatory markers play a role in the development as well as severity of Type 2 diabetes mellitus (T2DM). This study has been designed to decipher the involvement of C-Reactive Protein (CRP), Tumor Necrosis Factor (TNFα), Interleukin-6 (IL-6) and Interleukin-10 (IL-10) in the etiopathogenesis of T2DM.

Basic procedures: A total of 480 T2DM cases and 540 healthy controls were recruited for the study. Blood samples were collected from each study subject to measure the serum levels of CRP, TNFα, IL-6 and IL-10.

Main findings: We found that serum levels of CRP in mg/dl (4.2 ± 0.9), TNFα in pg/ml (34.5 ± 8.8), IL-6 in pg/ml (19.2 ± 7.6) in T2DM patients were significantly high as compared to control participants (CRP; 1.4 ± 0.6, TNFα; 12.7 ± 3.4, IL-6; 3.1 ± 1.4; P < 0.0001). The serum levels of IL-10 in pg/ml were lower in T2DM cases compared to controls (4.35 ± 1.2 vs. 9.6 ± 1.2). In addition, we observed a significant association of CRP levels with insulin resistance, obesity and dyslipidemia. Increased TNFα levels were strongly associated with female gender. Poor glycemic control and strong family history of diabetes. Poor glycemic control was significantly associated with elevated IL-6 levels. Moreover, significantly reduced IL-10 levels were found in T2DM patients with sedentary lifestyle; low educational and rural background.

Conclusions: This study showed a strong relationship between TNFα, IL-6, CRP, IL-10 and T2DM patients of Kashmiri ethnicity, treated at SMHS Hospital. Thus, supporting other studies and showing that cytokines may be good markers for T2DM development.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a group of genetically determined diseases which may be controlled by diet and/or hypoglycemic agents and/or exogenous insulin [1,2]. It accounts for about 90%–95% of all diagnosed cases of diabetes. T2DM, previously referred to as non-insulin dependent diabetes or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative insulin deficiency towards later stages [3]. T2DM is recognized as a serious public health concern with a considerable impact on human life and health expenditures. Rapid economic development and urbanization have led to a rising burden of diabetes in many parts of the world [4]. T2DM affects individuals' functional capacities and quality of life, leading to significant morbidity and premature mortality [5].

T2DM for the entire world is not an epidemic anymore but has covered into pandemic. Globally, an estimated 537 million adults aged 20–79 years are currently living with diabetes. The total number is predicted to rise to 643 million (11.3%) by 2030 and to 783 million (12.2%) by 2045 [6]. As far as human suffering (DALYs - Disability-Adjusted Life Years) are concerned, diabetes ranks as the 7th leading disease [7].

Among the countries of south-east Asia, India has highest number of people with diabetes in the age group of 20–79 years accounting to 74.2 million in 2021 with an age adjusted prevalence of 9.6%. There are estimated 39.4 million undiagnosed cases of diabetes in India as of 2021.

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India accounts for 1 in 7 of all adults living with diabetes worldwide [6]. According to a report published by Indian Council of Medical Research (ICMR) the prevalence rate of diabetes in Mountainous valley of Kashmir is 6.1% [8]. The global rise in diabetes mellitus is referred to population growth, ageing, increasing trends towards unhealthy diet, obesity and modern lifestyles [9]. It occurs usually in individuals over 30 years of age and dramatically increases as a result of changes in human behavior and increased body mass index [10].

Chronic low-grade inflammation is characterized by slightly elevated blood concentrations of acute-phase proteins, cytokines, and mediators with endothelial activation capacity [11]. It is likely that dysfunction of adipose tissue is a major contributor to chronic low-grade inflammation [11]. Besides adipose tissue, hyperglycaemia itself can contribute to chronic-sub clinical inflammation. Hyperglycaemia can stimulate the production of reactive oxygen species, which, in turn, stimulate production of pro-inflammatory cytokines, like TNFs and IL-6 [12]. Insulin, however, could counterbalance the pro-inflammatory effect of glucose by suppressing the production of the pro-inflammatory cytokines and by activating the production of anti-inflammatory cytokines, like interleukin 4 (IL-4) and IL-10 [13]. Ultimately, pro-inflammatory markers can contribute to insulin resistance through various mechanisms [11]. In addition, TNF and IL-6 also enhance oxidative stress by stimulation NF-kB or NADPH oxidase [12,13]. NF-kB causes a transcriptional response of genes involved in inflammatory processes [14]. A high concentration of IL-6 stimulates the production of CRP in the liver which is an acute-phase protein [15]. CRP is a non-specific inflammation marker that may contribute to insulin resistance by increasing phosphorylation of IRS [14] and by increasing the synthesis of cytokines like TNFs and IL-6 [16]. Although the role of anti-inflammatory cytokines in T2DM has received much less attention but IL-10 levels are known to be markedly reduced in T2DM patients [17,18].

Taken together, this suggests that low-grade inflammation may precede the development of T2DM and in turn is accompanied by dysfunctional inflammatory processes. On the other side, anti-inflammatory process is rather diminished. In order to strengthen the evidence-base for role of pro- and anti-inflammatory processes in T2DM, this study has been conceived to elucidate the role of key pro- and anti-inflammatory cytokines in the development and advancement of T2DM in Kashmiri population.

2. Materials and methods

2.1. Study design

This was a hospital based prospective study conducted by the Department of Biochemistry in collaboration with the Department of Medicine, Government Medical College and Associated SMHS Hospital from January 2019 to January 2022. The study procedure and informed consent were reviewed and sanctioned by the Institutional Ethical Committee of GMC Srinagar as per Helsinki declaration.

2.2. Study subjects and sample size

A total of four hundred eighty (n = 480) patients with T2DM, falling under criteria of American Diabetes Association (ADA-2016) [6], attending the Out Patient Department of Medicine were taken for the study. All the T2DM patients >30 years of age were included in the study. Patients with inflammatory diseases like inflammatory bowel syndrome, pancreatitis and autoimmune disorders which could affect the serum levels of inflammatory markers were excluded from the study. In addition, patients with advanced diabetes, any genetic disorder, cancer and gestational diabetes were also excluded from the study. In addition, five hundred forty (n = 540) healthy volunteers (age and sex matched), at least free from T2DM were taken as controls. The sampling of cases and controls was random in order to nullify the sampling bias. Written informed consent in vernacular (Urdu/Kashmiri) and working language (English) with questionnaire response from patients and healthy controls was taken on record. Sample size was calculated to detect an effect size of 0.40 at type 1 error of 50% and power of 80% using “G Power v. 3.1.9.2”.

2.3. Anthropometric measurement and body mass index (BMI)

Height (cm) was noted by a scale on wall and Weight (kg) was measured by digital weighing machine. Waist circumference (WC) was evaluated in the middle, between the lower rib margin and the iliac crest with subjects in upright position. BMI of subjects was calculated by formulae = weight (Kg)/height (m²). As per WHO classification the individuals were categorized according to their BMI (Kg/m²) as: Underweight, 18.5–24.99 = Normal, 25–29.99 = Preobese, 30–34.99 = Obese class I and 35–39.99 = Obese class II [19].

2.4. Sample collection

5 ml blood was collected by phlebotomists from T2DM patients and healthy controls through venipuncture after an overnight fast of at least 10–12 h. 3 ml of collected blood was immediately transferred into clot activator vials and centrifuged at 4000 rpm for 2 min and serum was aliquoted into 2 ml microfuge tubes. Further, 2 ml of whole blood was collected in EDTA containing vials for estimation of glycosylated hemoglobin (HbA1c). The whole blood and serum samples were stored at –20 °C till further analysis.

2.5. Quantitative biochemical analysis

Quantitative estimation of glucose (by hexokinase G-6-PDH method), HbA1c (by enzymatic method), TG (by glycerol phosphate oxidase method), total cholesterol (by enzymatic method), low density lipoprotein-cholesterol (LDL-C; by measured liquid selective detergent) and high density lipoprotein-cholesterol (HDL-C; by accelerator selective detergent) was performed using standard commercially available kits (Abbott, USA), employing the principle of spectrophotometry. Samples were processed and analysed on ARCHITECT C-4000 fully automated biochemistry analyser (Abbott, USA) in the Biochemistry Diagnostic Laboratory, SMHS Hospital Srinagar within 1–2 h after collection. The normal values of biochemical parameters were as: fasting blood glucose: 100–125 mg/dl; HbA1c: <6.5%, total cholesterol: ≤200 mg/dl; TG: ≤200 mg/dl; LDL-C: ≤120 mg/dl; HDL-C: ≥40 mg/dl (M) and ≥50 mg/dl (F).

2.6. Quantitative estimation of fasting insulin levels

Fasting Insulin levels (μIU/ml) of T2DM cases and controls were measured using chemiluminescent micro particle immunnoassay (CMIA) technology with flexible assay protocols, referred to as Chemillex. Serum samples were quantitatively analysed on ARCHITECT i2000 fully automatic immunnoassay analyser (Abbott, USA) within 1–2 h after collection, following the ARCHITECT insulin reagent kit (Abbott, USA) instructions. Insulin levels of 5–25 μIU/ml are considered to be normal [20].

2.7. Insulin resistance (IR)

HOMA-IR (Homeostatic Model Assessment–Insulin Resistance) was used to evaluate insulin resistance of study subjects using the formula [21]:

\[
\text{HOMA - IR} = \frac{\text{fasting serum insulin (μIU/ml) } \times \text{fasting plasma glucose (mmol/l)}}{22.5}
\]

On converting the units of fasting plasma glucose from mmol/l to mg/dl we multiplied the equation by a conversion factor of 1/18
The HOMA score of <1.9 was considered as indicator of “Insulin sensitivity”; 1.9 to 2.9 as indicator of “Low IR” and >2.9 as indicator of Significant IR [21].

2.8. Quantitative estimation of serum TNFα

Quantitative measurement of TNFα in serum was done by sandwich enzyme-linked immunosorbent assay (ELISA) using Diaclone Human TNFα ELISA kit following manufacturer’s protocol (Diaclone, France). The limit of quantitation was estimated to be 8 pg/ml. The coefficient of variation for TNFα was 3.3% and 9.0% (intra and inter-assay). Serum TNFα levels of 0–29.4 pg/ml were considered as “Normal” and >29.4 pg/ml as “Elevated” [22].

2.9. Quantitative estimation of serum IL-10

Quantitative measurement of IL-10 in serum was done by sandwich enzyme-linked immunosorbent assay (ELISA) using Diaclone Human IL-10 ELISA kit following manufacturer’s protocol (Diaclone, France). The limit of quantitation was estimated to be 4.9 pg/ml. The coefficient of variation for IL-10 was 7.5%. Serum IL-10 levels of 4.8–9.8 pg/ml were considered as “Normal” and <4.8 pg/ml as “Low” [23].

2.10. Quantitative estimation of serum CRP and IL-6

Serum CRP and IL-6 levels were quantitatively estimated by Chemiluminescence immunoassay (CLIA) technology using ARCHITECT i2000 fully automatic immunoassay analyser (Abbott, USA) within 1–2 h after collection, following the reagent kit instructions (Abbott, USA). Serum CRP levels of 0–12.4 mg/dl were taken as “Normal” whereas >12.4 mg/dl were “Elevated”. Serum IL-6 levels of 0–16.4 pg/ml were considered as “Normal” and >16.4 pg/ml as “Elevated” [22].

2.11. Statistical analysis

Binary Logistic regression analysis was used to decipher association of TNF, CRP, IL-6 and IL-10 levels with risk of disease. Analysis was done by student’s t-test and F-test (ANOVA). The relative risk was estimated by odds ratios (OR) and 95% confidence intervals (95% CI), P ≤ 0.05 was considered as significant. Statistical analysis was done using SPSS 23.0 statistical package (SPSS Inc., Chicago IL, USA).
cases (fasting blood sugar in mg/dl: 166.4 ± 31.9, 2 h OGTT in mg/dl: 314 ± 50.9, HbA1c%: 9.8 ± 2.8) was significantly higher as compared to healthy controls (fasting blood sugar in mg/dl: 80.9 ± 6.8, 2 h OGTT in mg/dl: 121.1 ± 8.2, HbA1c%: 4.7 ± 0.8) (P < 0.0001). HOMA-IR of T2DM cases was significantly higher as compared to controls (9.7 ± 2.6 vs. 1.5 ± 0.4; P < 0.0001) (Table 2).

3.3. Association of pro-and anti-inflammatory markers between T2DM cases and controls

Table 3 depicts the levels of TNFα, CRP, IL-6 and IL-10 in cases vs. controls. None of the pro- and anti-inflammatory markers were found to be elevated or reduced in controls. In contrast, CRP levels were elevated in all the T2DM patients (480 of 480; 100%). TNFα and IL-6 levels were found to be elevated in 66.3% (318 of 480) and 54.4% (261 of 480) of T2DM cases respectively. While as, IL-10 levels were reduced in 75.7% (363 of 480) of T2DM cases was significantly reduced compared to controls (9.7 ± 2.6 vs. 1.5 ± 0.4; P < 0.0001) (Table 2).

Table 4 contains the serum levels of pro- and anti-inflammatory markers in cases and controls. The serum CRP, TNFα and IL-6 levels of cases was significantly reduced compared to controls whereas IL-10 level was significantly reduced in T2DM cases compared to controls (P < 0.0001) (Table 4).

3.4. Stratification analysis of CRP levels in T2DM cases

All the T2DM patients with elevated CRP levels were having normal fasting insulin levels and significant insulin resistance (100%; P = 0.008).

When stratified with respect to BMI all the obese class 2 patients were having elevated levels of CRP (399 of 399; 100%) whereas none of the patients with normal BMI were having elevated TNFα levels (P = 0.009). Table 5 illustrates the association of serum CRP levels with various demographic and biochemical characteristics of T2DM cases.

3.5. Stratification analysis of TNFα levels in T2DM cases

Table 6 portrays the association of serum TNFα levels with various demographic and biochemical characteristics of T2DM cases. TNFα levels were significantly elevated in 74.6% (177 of 237) of females as compared to only 58.0% (121 of 213) of males with T2DM (P < 0.0001). Significantly higher number of cases with family history of T2DM were having elevated levels of TNFα as compared to those without family history of T2DM (69.0% vs 60.9%; P = 0.3). Similarly, most of the T2DM patients with poor glycemic control were having significantly elevated TNFα levels as compared to patients having well controlled glycemic index (95.4% vs. 46.8%).

3.6. Stratification analysis of IL-6 levels in T2DM cases

Table 7 shows the association of serum IL-6 levels with various demographic and biochemical characteristics of T2DM cases. Illiterate patients were having elevated levels of IL-6 as compared to literate patients (59.4% vs 45.7%; P = 0.004), 62.5% (120 of 192) of T2DM patients with poor glycemic control (HbA1c% >9) were having elevated IL-6 levels as compared to patients having well controlled glycemic index (48.9%; 141 of 288).

3.7. Stratification analysis of IL-10 levels in T2DM cases

IL-10 levels were reduced in 71.3% (219 of 273) of rural inhabitants as compared to only 69.1% (144 of 207) of urban inhabitants with T2DM and the difference was significant (P = 0.01). Higher number of T2DM patients with sedentary lifestyle (81% vs 267 of 330) were having significantly reduced levels of IL-10 as compared to those having active lifestyle (64.0%; 96 of 150; P < 0.0001). In addition, 79.3% of illiterate T2DM patients were having low IL-10 levels while as 69.5% of literate T2DM cases were having low IL-10 levels and the difference was statistically significant (P = 0.02). Table 8 shows the association of demographic and biochemical characteristics of T2DM cases with serum IL-10 levels.

3.8. Interrelation between pro- and anti-inflammatory markers

Table 7 depicts the relationship between IL-6 and IL-10. We observed a significant negative association between IL-6 and IL-10 levels. Among cases with low IL-10 levels, 61.9% were having elevated IL-6 levels. On
the contrary, among cases with normal serum IL-10 levels only 30.7% were having elevated IL-6 levels (P < 0.0001).

4. Discussion

T2DM a non-communicable disease, is a leading cause of premature deaths worldwide and a major threat to health system and economy of countries [7]. In recent years, male sex has been regarded as a risk factor for the development of T2DM [24] which is in line with our observation due to the increasing prevalence of obesity in men than in women [25]. Although, numerous studies support the fact that increasing age plays an important role in the development of T2DM [26], the majority of T2DM cases, in our study, were of lower age group (<50 years), which is in agreement with few other studies performed in different populations [27]. In the national survey 54.1% of Indian diabetic population developed the disease in the most productive years of their lives i.e. before the age of 50 years and they also had a higher risk of developing chronic complications of diabetes [28]. There were more smokers in diabetic group compared to controls (21.3% vs. 2.7%; P < 0.0001). According to the US Department of Health and Human Services (USDHHS) factsheet on Smoking and Diabetes, Smokers are 30%-40% more likely to develop T2DM than non-smokers [28,29]. Smoking can dysregulate insulin levels as high levels of nicotine can lessen the effectiveness of insulin, causing smokers to need more insulin for regulation of blood sugar levels [29]. Smoking also increases inflammation and oxidative stress [30], to directly damage β-cell function [31] and to impair endothelial function [32]. About 69.0% of enrolled patients were having sedentary lifestyle compared to 41.7% of controls (P < 0.0001) which is in line with majority of the studies across globe associating sedentary lifestyle and reduced physical activity with the development and severity of T2DM [33,34]. In our study, 63.2% of T2DM cases were illiterates compared 45.0% of controls (P < 0.0001) with low literacy being the major factor of illiteracy [35]. Most of the enrolled cases (68.2%) had family history of T2DM in first degree relatives. It has been established that patients with a positive family history of diabetes experience 3- to 4-fold higher risk of developing this disease [36], and the risk of diabetes increases with the number of affected relatives [36]. HbA1c (%) reflects the glycemic control of an individual and 60% of our set of patients had well controlled glycemic index compared to only 40% which were having poor glycemic control (P < 0.0001). We speculate, that most of the patients were freshly diagnosed cases of T2DM who had not proceeded to an advanced disease. Although fasting insulin levels were normal in all cases as well as all controls but there was a significant insulin resistance noted in all the T2DM cases (P < 0.0001). Muscle insulin resistance is clearly a risk factor for development of T2DM [37]. In this study it was found that the lipid profile parameter: triglycerides (TG), total cholesterol (TC), high density lipoproteins (HDL) and low density lipoproteins (LDL) were significantly increased in the T2DM cases as compared to healthy controls, suggesting that elevated levels of lipid parameters lead to dyslipidemia, which may plays a role in the development and progression of T2DM in this ethnic population and same has been confirmed by previous studies in different populations study done by Ozder et al. in Turkish population, where in they observed that lipid profile parameters were highly increased in the T2DM patients [38]. High triglycerides and cholesterol levels in T2DM cases predisposes T2DM patients at the risk of diabetic complications like cardiovascular problems [38].

In our study we observed a significantly higher levels of TNFα, CRP and IL-6 in serum of T2DM cases compared to controls. Levels of TNFα, CRP and IL-6 were found to be normal in all the controls. In large case control studies elevated serum levels of TNFα, IL-6 and CRP were elevated in T2DM patients as compared to healthy controls and significantly associated with the risk of developing T2DM and its related complications [39].

CRP is a common marker of sub clinical inflammation and an acute phase reactant leading to over expression of cytokines like TNFα and IL-6 [40]. In our study, CRP levels were elevated in all the T2DM patients. Elevation in CRP levels is usually associated with T2DM [41]. A study conducted on Korean population reported higher serum CRP levels in T2DM patients as compared to healthy controls and predicted CRP as an independent biomarker for assessment of sub clinical Inflammation and hence T2DM [42]. Several other studies carried on different populations have also reported higher CRP levels in T2DM patients [43,44]. When stratified, higher CRP levels were found to be associated with significant insulin resistance. CRP is an early risk factor for the development of insulin resistance and plays a critical role in pathogenesis of T2DM by its action on pancreatic β-cells [42]. We observed that obesity is the major determinant of elevated CRP in subjects with T2DM. There is a close relationship between circulating CRP concentrations and anthropometric measures of obesity [45]. Since the synthesis of CRP by the liver is predominantly regulated by interleukin-6, [46] it is believed that interleukin-6 originating from adipose tissue contributes to the raised CRP concentrations in obese insulin-resistance subjects. TNFα does not induce CRP directly, but can potentiate the induction of CRP by IL-6 [47]. In our study, high levels of CRP were significantly associated with dyslipidemia in T2DM patients. Many studies from different populations have noted a statistically significant relationship between the concentration of CRP and the occurrence of dyslipidemia in T2DM [48,49]. However, according to a previous study, higher CRP levels were not associated with elevated concentrations of lipid parameters [50].

Findings of our study exhibit that increased level of pro-inflammatory biomarkers such as TNFα and IL-6 are strongly associated with the development of T2DM which is in concurrence with the studies done in different populations [51,52]. Elevated blood glucose levels promote inflammation by increasing oxidative stress due to formation of advanced glycation end products (AGE) and increased pro-inflammatory cytokines like TNFα, IL-6 etc. [53]. Recently, a meta-analysis of nineteen studies reported that the elevated levels of pro-inflammatory cytokines, including TNFα, IL-6 were strongly associated with increased risk to occurrence of T2DM [44]. Alazm et al. confirmed our findings and reported correlation of TNFα with T2DM cases in Saudi Arabian population [54]. On stratification it was found that TNFα levels were significantly associated with female gender in T2DM patients. Females have higher percentage of adipose tissue compared to males and TNFα, an adipocytokine, is produced by adipose tissues [55], which indicates that females would produce higher levels of TNFα as compared to their male counterparts [55]. In the present study, higher TNFα levels were significantly associated with family history of T2DM. Maltezos et al. showed that

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Table 4. Levels of serum pro-inflammatory markers (mean ± SD) in cases vs. controls.

| Pro-inflammatory markers | Controls Mean ± SD (Range) | Cases Mean ± SD (Range) | P value |
|--------------------------|-----------------------------|--------------------------|---------|
| Serum CRP levels (mg/dl) | 1.4 ± 0.6 (0.3-2.8)         | 4.2 ± 0.9 (2.5-8.0)      | <0.0001 |
| Serum TNFα levels (pg/ml)| 12.7 ± 3.4 (5.0-22.5)       | 34.5 ± 8.8 (16.8-55.8)   | <0.0001 |
| Serum IL-6 levels (pg/ml)| 3.1 ± 1.4 (0.9-8.2)         | 19.2 ± 7.2 (8.4-36.9)    | <0.0001 |
| Serum IL-10 levels (pg/ml)| 9.6 ± 1.2 (6.8-12.5)        | 4.35 ± 1.2 (2.1-7.7)     | <0.0001 |

TNFα: Tumor necrosis factor, CRP: C-reactive protein, IL: Interleukins.
descendants of patients with T2DM have higher TNFα levels compared to descendants of non-diabetic individuals [56]. We observed a very strong association of increased TNFα and IL-6 levels with Poor glycemic control (HbA1c% > 9) in T2DM cases. Mirza et al. reported that TNFα was most significantly elevated in the group of patients with HbA1c values higher than 6.5% [52,55]. Our study is in agreement with a previous study done in Pakistani population, wherein they reported significant association between elevated levels of IL-6 and glycemic profile [57].

IL-10 effectively prevents the production of pro-inflammatory cytokines such as IL-6 and TNFα hence has strong deactivating properties on the inflammatory host response mediated by macrophages and lymphocytes [58]. We report a significantly lower levels of IL-10 in serum of...
### Table 6: Association of TNFα levels with various demographic and biochemical characteristics of cases and controls.

| Characteristics of Cases | Serum TNFα levels in Cases | OR (95% CI) | P value |
|--------------------------|----------------------------|-------------|---------|
|                          | Normal (162 (33.7))        | Elevated (318 (66.3)) |          |
| Gender                   | 243 (50.6)                 | 102 (42.0)   | 141 (58.0) | Ref. (1.00) |
|                         | Female                     | 237 (49.4)   | 60 (25.4) | 177 (74.6) | 2.1 (1.4-3.1) |
| Age in years             | ≤50                        | 294 (61.2)   | 96 (32.6) | 198 (67.4) | Ref. (1.00) |
|                         | >50                        | 186 (38.8)   | 66 (35.5) | 120 (64.5) | 0.9 (0.6-1.2) |
| Dwelling                 | Urban                      | 207 (43.1)   | 63 (30.4) | 144 (69.5) | Ref. (1.00) |
|                         | Rural                      | 273 (56.9)   | 99 (36.2) | 174 (63.7) | 0.7 (0.5-1.1) |
| Smoking status           | Non-smoker                 | 330 (68.7)   | 111 (33.6) | 219 (66.3) | Ref. (1.00) |
|                         | Smoker                     | 150 (21.3)   | 51 (34.0) | 99 (66.0) | 0.98 (0.6-1.4) |
| Lifestyle                | Active                     | 150 (31.2)   | 39 (26.0) | 111 (74.0) | Ref. (1.00) |
|                         | Sedentary                  | 330 (68.8)   | 123 (37.2) | 207 (62.7) | 0.6 (0.4-0.9) |
| Education                | Literate                   | 177 (36.8)   | 30 (16.9) | 147 (83.0) | Ref. (1.00) |
|                         | Illiterate                 | 303 (63.2)   | 132 (43.5) | 171 (56.4) | 0.26 (0.1-0.4) |
| Family history           | No                         | 150 (31.2)   | 60 (40.0) | 90 (60.0) | Ref. (1.00) |
|                         | Yes                        | 330 (68.2)   | 102 (30.9) | 228 (69.0) | 1.5 (1.02-2.2) |
| HbA1c                    | 6.5–9.0 (Well controlled)  | 288 (60.0)   | 153 (53.1) | 135 (46.8) | Ref. (1.00) |
|                         | >9 (Poor glycemic control) | 192 (39.5)   | 9 (4.6) | 183 (95.4) | 23.0 (11.3-46.7) |
| Fasting Insulin levels   | Normal                     | 480 (100)    | 162 (33.7) | 318 (66.2) | Ref. (1.00) |
|                         | Low                        | 00 (0.0)     | 00 (0.0) | 00 (0.0) | 0.51 (0.01-19.9) |
| HOMA IR                  | Insulin sensitive          | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Low IR                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | 1.0 (0.02-50.3) | 0.9 |
|                         | Significant IR             | 480 (100)    | 162 (33.7) | 318 (66.3) | 1.9 (0.05-7.6) | 0.6 |
| BMI                      | Normal                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Underweight                | 00 (0.0)     | 00 (0.0) | 00 (0.0) | 1.0 (0.02-50.3) | 0.9 |
|                         | Preobese                   | 30 (6.2)     | 06 (20.0) | 24 (80.0) | 3.7 (0.08-16.1) | 0.4 |
|                         | Obese Class I              | 51 (10.6)    | 18 (35.2) | 33 (64.7) | 1.8 (0.04-7.3) | 0.7 |
|                         | Obese Class II             | 399 (83.1)   | 138 (34.5) | 261 (65.4) | 1.8 (0.04-7.4) | 0.7 |
| TG                       | Normal                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Elevated                   | 480 (100)    | 162 (33.7) | 318 (66.3) | 1.9 (0.05-7.6) | 0.6 |
| Total Cholesterol        | Normal                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Elevated                   | 480 (100)    | 162 (33.7) | 318 (66.3) | 1.9 (0.05-7.6) | 0.6 |
| LDL-C                    | Normal                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Elevated                   | 480 (100)    | 162 (33.7) | 318 (66.3) | 1.9 (0.05-7.6) | 0.6 |
| HDL-C                    | Normal                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Elevated                   | 480 (100)    | 162 (33.7) | 318 (66.3) | 1.9 (0.05-7.6) | 0.6 |
| Serum CRP levels         | Normal                     | 00 (0.0)     | 00 (0.0) | 00 (0.0) | Ref. (1.00) |
|                         | Elevated                   | 480 (100.0)  | 162 (33.7) | 318 (66.3) | 1.9 (0.05-7.6) | 0.6 |
| Serum IL-6 levels        | Normal                     | 219 (45.6)   | 69 (31.5) | 150 (68.4) | Ref. (1.00) |
|                         | Elevated                   | 261 (54.4)   | 93 (35.6) | 168 (64.4) | 0.8 (0.5-1.2) |
| Serum IL-10 levels       | Normal                     | 117 (24.3)   | 21 (17.9) | 96 (82.0) | Ref. (1.00) |
|                         | Low                        | 363 (75.6)   | 141 (38.8) | 222 (61.2) | 0.3 (0.2-0.6) |

HOMA IR; Homeostatic model assessment–Insulin Resistance, BMI; Body mass index, TG; Triglycerides, LDL-C; Low density lipoproteins-cholesterol, HDL-C; High density lipoproteins-cholesterol, TNF; Tumor necrosis factor, CRP; C-reactive protein, IL; Interleukins
Table 7. Association of Serum IL-6 levels with various demographic and biochemical characteristics of cases and controls.

| Characteristics of Cases | N = 480 (%) | Serum IL-6 levels in Cases | OR (95% CI) | P value |
|--------------------------|-------------|---------------------------|-------------|---------|
|                          |             | Normal 219 (45.6)         | Elevated 261 (54.4) |         |
| Gender                   |             |                           |              |         |
| Male                     | 243 (50.6)  | 111 (45.6)                | 132 (54.4)   | Ref. (1.00) |
| Female                   | 237 (49.4)  | 108 (45.6)                | 129 (54.4)   | 1.004 (0.7-1.4) |
| Age in years             |             |                           |              |         |
| ≤50                      | 294 (61.2)  | 126 (42.8)                | 168 (57.1)   | Ref. (1.00) |
| >50                      | 186 (38.8)  | 93 (50.0)                 | 93 (50.0)    | 0.7 (0.5-1.08) |
| Dwelling                 |             |                           |              |         |
| Urban                    | 207 (43.1)  | 96 (46.3)                 | 111 (53.6)   | Ref. (1.00) |
| Rural                    | 273 (56.9)  | 123 (45.0)                | 150 (54.9)   | 1.05 (0.7-1.5) |
| Smoking status           |             |                           |              |         |
| Non-smoker               | 330 (68.7)  | 141 (42.7)                | 189 (57.2)   | Ref. (1.00) |
| Smoker                   | 150 (21.3)  | 78 (52.0)                 | 72 (48.0)    | 0.7 (0.4-1.01) |
| Lifestyle                |             |                           |              |         |
| Active                   | 150 (31.2)  | 66 (44.0)                 | 84 (56.0)    | Ref. (1.00) |
| Sedentary                | 330 (68.8)  | 153 (46.3)                | 177 (53.6)   | 0.9 (0.6-1.3) |
| Education                |             |                           |              |         |
| Literate                 | 177 (36.8)  | 96 (51.9)                 | 81 (48.1)    | Ref. (1.00) |
| Illiterate               | 303 (63.2)  | 123 (40.5)                | 180 (59.5)   | 1.7 (1.2-2.5) |
| Family history           |             |                           |              |         |
| No                       | 150 (31.2)  | 63 (42.0)                 | 87 (58.0)    | Ref. (1.00) |
| Yes                      | 330 (68.8)  | 156 (47.2)                | 174 (52.7)   | 0.8 (0.5-1.2) |
| HbA1c                    |             |                           |              |         |
| 6.5-9.0 (Well controlled)| 288 (60.0)  | 147 (51.0)                | 141 (49.9)   | Ref. (1.00) |
| >9 (Poor glycemic control)| 192 (39.5)  | 72 (37.5)                 | 120 (62.5)   | 17 (1.2-2.5) |
| Fasting Insulin levels   |             |                           |              |         |
| Normal                   | 480 (100)   | 219 (45.6)                | 261 (54.4)   | Ref. (1.00) |
| Low                      | 00 (0.0)    | 00 (0.0)                  | 00 (100.0)   | 0.8 (0.02-32.9) |
| HOMA IR                  |             |                           |              |         |
| Insulin sensitive        | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Low IR                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | 1.0 (0.02-50.3) |
| Significant IR           | 480 (100)   | 219 (45.6)                | 261 (54.4)   | 1.2 (0.03-46.6) |
| BMI                      |             |                           |              |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Underweight              | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | 1.0 (0.02-50.3) |
| Preobese                 | 30 (6.2)    | 15 (50)                   | 15 (50)      | 1.0 (0.01-41.3) |
| Obese Class I            | 51 (10.6)   | 24 (47.0)                 | 27 (53.0)    | 1.1 (0.02-45.2) |
| Obese Class II           | 399 (83.1)  | 180 (45.1)                | 219 (54.8)   | 1.2 (0.03-47.6) |
| TG                       |             |                           |              |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Elevated                 | 480 (100)   | 219 (45.6)                | 261 (54.3)   | 1.2 (0.03-46.6) |
| Total Cholesterol        |             |                           |              |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Elevated                 | 480 (100)   | 219 (45.6)                | 261 (54.3)   | 1.2 (0.03-46.6) |
| LDL-C                    |             |                           |              |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Elevated                 | 480 (100)   | 219 (45.6)                | 261 (54.3)   | 1.2 (0.03-46.6) |
| HDL-C                    |             |                           |              |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Low                      | 480 (100)   | 219 (45.6)                | 261 (54.3)   | 1.2 (0.03-46.6) |
| Serum CRP levels         |             |                           |              |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)     | Ref. (1.00) |
| Elevated                 | 480 (100.0) | 219 (45.6)                | 261 (54.3)   | 1.2 (0.03-46.6) |
| Serum IL-10 levels       |             |                           |              |         |
| Normal                   | 117 (24.3)  | 81 (69.2)                 | 36 (30.7)    | Ref. (1.00) |
| Low                      | 363 (75.6)  | 138 (38.0)                | 225 (61.9)   | 3.6 (2.3-5.7) |

HOMA IR; Homeostatic model assessment–Insulin Resistance, BMI; Body mass index, TG; Triglycerides, LDL-C; Low density lipoproteins-cholesterol, HDL-C; High density lipoprotein-cholesterol, TNF; Tumor necrosis factor, CRP, C-reactive protein, IL; Interleukins.
T2DM cases compared to controls in which IL-10 levels were found to be in normal range. Although not much research has been done on the elucidation of relationship between IL-10 levels and T2DM, Leiden 85-Plus Study showed that production of low levels of IL-10 is associated with T2DM and other related co-morbidities [59]. By counter-regulating the effects of TNFα and IL-6, high levels of IL-10 cause an upregulation of tyrosine kinase activity of the insulin receptor and confer protection against T2DM, whereas a low IL-10 production capacity would

| Characteristics of Cases | N = 480 (%) | Serum IL-10 levels in Cases | OR (95% CI) | P value |
|--------------------------|-------------|----------------------------|-------------|---------|
|                          | Normal 117 (24.3) | Low 363 (75.7) |             |         |
| **Gender**               |             |                           |             |         |
| Male                     | 243 (50.6)  | 54 (22.2)                 | 189 (77.8)  | Ref. (1.00) |
| Female                   | 237 (49.4)  | 63 (26.5)                 | 174 (73.5)  | 0.8 (0.5-1.2) |
| **Age in years**         |             |                           |             |         |
| ≤50                      | 294 (61.2)  | 66 (22.4)                 | 228 (77.6)  | Ref. (1.00) |
| >50                      | 186 (38.8)  | 51 (27.4)                 | 135 (72.6)  | 0.7 (0.5-1.1) |
| **Dwelling**             |             |                           |             |         |
| Urban                    | 207 (43.1)  | 63 (30.4)                 | 144 (69.1)  | Ref. (1.00) |
| Rural                    | 273 (56.9)  | 54 (19.7)                 | 219 (71.3)  | 1.7 (1.1-2.7) |
| **Smoking status**       |             |                           |             |         |
| Non-smoker               | 330 (68.7)  | 69 (20.9)                 | 261 (79.1)  | Ref. (1.00) |
| Smoker                   | 150 (21.3)  | 48 (32.0)                 | 102 (68.0)  | 0.5 (0.3-0.8) |
| **Lifestyle**            |             |                           |             | <0.0001 |
| Active                   | 150 (31.2)  | 54 (36.0)                 | 96 (64.0)   | Ref. (1.00) |
| Sedentary                | 330 (68.8)  | 63 (19.0)                 | 267 (81.0)  | 2.3 (1.5-3.6) |
| **Education**            |             |                           |             |         |
| Literate                 | 177 (36.8)  | 54 (30.5)                 | 123 (69.5)  | Ref. (1.00) |
| Illiterate               | 303 (63.2)  | 63 (20.7)                 | 240 (79.3)  | 1.6 (1.1-2.5) |
| **Family history**       |             |                           |             |         |
| No                       | 150 (31.2)  | 30 (20.0)                 | 120 (80.0)  | Ref. (1.00) |
| Yes                      | 330 (68.2)  | 87 (26.3)                 | 243 (73.7)  | 0.7 (0.4-1.1) |
| **HbA1c**                |             |                           |             |         |
| 6.5–9.0 (Well controlled)| 288 (60.0)  | 66 (22.9)                 | 222 (77.1)  | Ref. (1.00) |
| >9 (Poor glycemic control)| 192 (39.5)  | 51 (26.5)                 | 141 (73.5)  | 0.8 (0.5-1.2) |
| **Fasting Insulin levels**|             |                           |             |         |
| Normal                   | 480 (100)   | 117 (24.3)                | 363 (75.7)  | Ref. (1.00) |
| Low                      | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | 0.3 (0.008-12.7) |
| **BMI**                  |             |                           |             |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | Ref. (1.00) |
| Underweight              | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | 1.0 (0.02-50.3) |
| Obese Class I           | 30 (6.2)    | 09 (30.0)                 | 21 (70.0)   | 2.1 (0.05-89.4) |
| Obese Class II          | 399 (83.1)  | 90 (22.5)                 | 309 (77.5)  | 3.3 (0.08-133.2) |
| **TG**                  |             |                           |             |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | Ref. (1.00) |
| Elevated                 | 480 (100)   | 117 (24.3)                | 363 (75.7)  | 3.1 (0.07-120.6) |
| **Total Cholesterol**    |             |                           |             |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | Ref. (1.00) |
| Elevated                 | 480 (100)   | 117 (24.3)                | 363 (75.7)  | 3.1 (0.07-120.6) |
| **LDL-C**                |             |                           |             |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | Ref. (1.00) |
| Elevated                 | 480 (100)   | 117 (24.3)                | 363 (75.7)  | 3.1 (0.07-120.6) |
| **HDL-C**                |             |                           |             |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | Ref. (1.00) |
| Elevated                 | 480 (100)   | 117 (24.3)                | 363 (75.7)  | 3.1 (0.07-120.6) |
| **Serum CRP levels**     |             |                           |             |         |
| Normal                   | 00 (0.0)    | 00 (0.0)                  | 00 (0.0)    | Ref. (1.00) |
| Elevated                 | 480 (100)   | 117 (24.3)                | 363 (75.7)  | 3.1 (0.07-120.6) |

HOMA IR; Homeostatic model assessment–Insulin Resistance, BMI; Body mass index, TG; Triglycerides, LDL-C; Low density lipoproteins-cholesterol, HDL-C; High density lipoproteins-cholesterol, TNF; Tumor necrosis factor, CRP; C-reactive protein, IL; Interleukins.
predispose individuals to T2DM [59,60]. On stratification, IL-10 levels were markedly reduced in T2DM patients who were having sedentary lifestyle. Higher accumulated amount of sedentary time has been related to lower levels of anti-inflammatory biomarker IL-10 [61]. The results have been further substantiated by previous findings showing higher levels of IL-10 gene expression in active compared to sedentary individuals [62]. Mostly, due to the reason that elevations in IL-10 is associated with a reduction in adiposity by physical activity [61]. Further, IL-10 levels were significantly reduced in rural dwellers and illiterate individuals having T2DM. We speculate that the illiterate rate is more in rural areas and people are ignorant and receive less medical care and may have undiagnosed T2DM leading to more complications which could lead to increase in pro-inflammatory markers and a relative decrease in anti-inflammatory markers like IL-10.

In our study, we observed significantly decreased levels of IL-10 with increase in IL-6 levels. It has been maintained previously that IL-10 blocks the IL-6 production by T-cells via a monocyte and IL-2 independent mechanism [63]. So, in scarcity of IL-10 the IL-6 levels are increased in our population having T2DM.

4.1. Strength of the study

The strength of this study include the systematic recruitment of subjects and controls and rigorous assessment of biochemical, inflammatory and anthropometric parameters.

4.2. Limitation of the study

Our study is limited since it is a single-center study with modest sample size.

5. Conclusion

A significant increase in pro-inflammatory markers in patients with T2DM suggest their role as underlying factor for the development of T2DM. In addition, a significant decrease in anti-inflammatory markers in T2DM suggest their protective role towards disease predisposition. Pro-inflammatory markers, in particular, have been strongly associated with Insulin resistance, glycemic control, adiposity, lifestyle and dyslipidemia in T2DM patients which suggests coexistence of dysregulated lipid metabolism and inflammation which may lead to more advanced disease. Our observation may help to highlight the need for serious monitoring of pro- and anti-inflammatory biomarkers in patients with T2DM for their proper management.

Declarations

Author contribution statement

Haamid Bashir: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Sabihai Majid: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.
Mosin Saleem Khan: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Mohammad Hayat Bhat, Rabia Hamid and Roohi Ashraf: Contributed reagents, materials, analysis tools or data.
Sunia Faiz: Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interest’s statement

The authors declare no conflict of interest.

Additional information

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References

[1] L. Gropu, T. Tuomi, M. Bowley, P. Zimmer, I.R. Mackay, Latent autoimmune diabetes in the adults (LADA) more than a name, Diabetologia 49 (2006) 1996–1998.
[2] R. Ashraf, M.S. Khan, S. Lone, M. Bhat, S. Rashid, S. Majid, H. Bashir, Implication of Leptin and leptin receptor gene Variations in type 2 diabetes mellitus: a case-control study, J Endocrinol Metab 12 (1) (2022) 19–31.
[3] IDF Diabetes Atlas 2021. https://diabetesatlas.org/resources/.
[4] E.M. Onyango, B.M. Onyango, The rise of noncommunicable diseases in Kenya: an examination of the time trends and contribution of the changes in diet and physical activity, J. Epidemiol. Glob. Health 8 (2018) 1–7.
[5] R. Ramtabal, C. Khan, K.K. Maharaj, S. Nallamothu, A. Hinds, A. Dhanoa, H.C. Yeh, F. Hill-Briggs, M. Lazo, Prevalence of self-reported sleep disturbance and sleep habits in type 2 diabetes patients in South Trinidad, J. Epidemiol. Glob. Health 1 (2015) S25–S43.
[6] American Diabetes Association; 2, Classification and Diagnosis of Diabetes Care 39 (1) (2016) S13–S22.
[7] M.A.B. Khan, M.J. Hashim, J.K. King, R.D. Govender, H. Mustafa, J. Al Kaabi, Epidemiology of Type 2 diabetes - global burden of disease and forecasted trends, J. Epidemiol. Glob. Health 10 (2020) 107–111.
[8] R.M. Arjana, M. Deepa, R. Pradeepa, J. Mahanta, K. Narain, H.K. Das, P. Adhikari, P.V. Rao, B. Sahoo, A. Kumar, A. Bhansali, M. John, R. Luza, T. Reang, S. Ningombam, L. Jampa, B.O. Budnab, N. Elangovan, R. Subashini, U. Venkatesan, R. Unnikrishnan, A.K. Das, S.V. Madhu, M.K. Ali, A. Pandey, R.S. Dhaliwal, T. Kaur, S. Swaminathan, MohanV, Prevalence of diabetes and prediabetes in 15 states of India: results from the ICMR-INDIAB population-based cross-sectional study, Lancet Diabetes Endocrinol 5 (2017) 585–596.
[9] K.A. Ahmed, S. Muniandy, I.S. Ismail, Type 2 diabetes and vascular complications: a group pathophysiologic view, Biomed. Res. 21 (2010) 147–155.
[10] P.J. Elmer, J.B. Brown, G.A. Nichols, G. Oster, Effects of weight gain on medical care costs, Int. J. Obes. Relat. Metab. Disord. 28 (2004) 1365–1373.
[11] M.S. Burhans, D.K. Hagman, J.N. Kuzma, K.A. Schmidt, M. Kritz, Contribution of adipose tissue inflammation to the development of type 2 diabetes mellitus, Compr. Physiol. 9 (2018) 1–58.
[12] U.N. Das, Molecular Basis of Health and Disease, Springer, 2011.
[13] H. Igra, R.M. Shariq, A.M. Shahnaz, N. Mudassar, G. Khalid, A.G. Bashir, Type 2 diabetes mellitus: from a metabolic disorder to an inflammatory condition, World J. Diabetes 6 (2015) 598–612.
[14] S. Devaraj, U. Singh, I. Jialal, Human C-reactive protein and the metabolic syndrome, Curr. Opin. Lipidol. 20 (2009) 182–189.
[15] M.B. Pepys, G.M. Hirschfeld, C-reactive protein: a critical update, J. Clin. Invest. 111 (2003) 1805–1812.
[16] D. Hanriot, G. Bello, A. Ropers, C. Seguin-Devaux, G. Poitevin, S. Grousse, V. Latger-Cannard, Y. Devaux, F. Zannad, RegnauV, P. Lacolley, P.M. Meriet, K. Hess, D. Longrois, Creactive protein induces pro- and anti-inflammatory effects, including, activation of the liver X receptor alpha, on human monocytes, Thromb. Haemostasis 99 (2007) 558–569.
[17] M. Gao, C. Zhang, Y. Ma, L. Bu, L. Yan, D. Liu, Hydrodynamic delivery of mIL10 gene protects mice from high-fat diet-induced obesity and glucose intolerance, Mol. Ther. 21 (2013) 1852–1861.
[18] E.G. Hong, H.J. Ko, Y.R. Cho, H.J. Ko, Z. Ma, T.Y. Yu, R.H. Friedline, E. Kurt-Jones, R. Finnberg, M.A. Fischer, E.L. Granger, C.C. Norbury, S.D. Hauschka, W.M. Philbrick, C.G. Lee, J.A. Elia, J.K. Kim, Interleukin-10 prevents diet-induced insulin resistance by attenuating macrophage and cytokine response in skeletal muscle, Diabetes 58 (2009) 2525–2535.
[19] R. Ashraf, T. Hassan, S. Rashid, To study the prevalence of metabolic syndrome in the adult population of Kashmir, Int. J. Sci. Res. 7 (2018) 60–65.
[20] S. Melmed, K.S. Polonsky, P.R. Larsen, H.M. Kronenberg, Williams Textbook of Endocrinology, thirteenth ed., 2016.
[21] M. Vogeser, D. König, I. Frey, H.G. Preidel, K.G. Pathoer, A. Berg, Fasting serum insulin and the homeostasis model of insulin resistance (HOMA-IR) in the
