Advances in BioScience
E-ISSN: 2583-0058
Volume 13, Issue 2, April 2022
PP 1-7
https://e-journal.sospublication.co.in

Original Article

Open Access

Detection of Insulin Resistance in Normoglycemic First-Degree Relatives of Type 2 Diabetics: A Case-Control Study

Kamalakar Bhagwat Mane[1,*], Shilpa Balaji Asegaonkar[2], Swati Digambar Sawant[3]

[1*]*MD-Biochemistry, Associate Professor & Head,* [3]*MD-Biochemistry, Assistant Professor, Department of Biochemistry, Dr. V. M. Government Medical College, Solapur, Maharashtra, India.*
[2]*MD-Biochemistry, Assistant Professor, Department of Biochemistry, Government Medical College, Aurangabad, Maharashtra, India.*

Keywords

Normoglycemic
Insulin
HOMA-IR
Diabetes Mellitus
First-degree relatives

Abstract

Background: Diabetes has a strong familial aggregation in Asian Indians, with a high prevalence among the first-degree relatives and vertical transmission through two or more generations. First-degree relatives of T2DM are at significant risk for developing T2DM.

Aim: Evaluation of insulin resistance in normoglycemic first-degree relatives of type 2 diabetic patients.

Methods: A total of 200 subjects were divided into two groups A and B. Group A comprises non-diabetic first-degree relatives of T2DM patients between the age group of 20 to 50 years. Group B comprises healthy controls without a family history of T2DM. Subjects were analyzed for fasting plasma glucose level, fasting serum Insulin and fasting serum hs-CRP.

Result: The mean value of blood sugar level did not show a significant difference between cases and controls (92.02 ± 9.23 vs. 91.77 ± 7.99; $p > 0.05$). The mean values of insulin (12.52 ± 3.65 vs. 5.08 ± 1.42), HOMA-IR (2.86 ± 0.95 Vs. 1.15 ± 0.34) and hs-CRP (2.4 ± 1.98 vs. 1.0 ± 0.38) (all $p < 0.001$) increased in cases as compared to controls. Fasting serum insulin shows a positive correlation with HOMA-IR and hs-CRP ($p < 0.001$). HOMA-IR strongly correlates with hs-CRP and shows a positive correlation ($p < 0.05$). Insulin and HOMA-IR shows strong positive correlation with each other ($r = 0.94$; $p < 0.001$).

Conclusion: Normoglycemic first-degree relatives of type 2 diabetic patients were insulin resistant compared to individuals without a family history of type 2 diabetes.

1 Introduction

Diabetes mellitus (DM) and its complexity have grown into the foremost important and challenging contemporary unhealthiness. Globally 380 million adults worldwide will have diabetes by 2025 and in India, this figure is expected to extend to 70 million by 2025 [1]. Diabetes has progressed from a minor ailment affecting the elderly to one of the leading causes of morbidity and mortality among young and middle-aged adults in the last 30 years [2]. The onset of Type 2 diabetes mellitus (T2DM) at an early age heralds several years of disease and an increased risk of the entire range of both microvascular and macrovascular complications will take place when affected individuals are still relatively young [3]. Thus, further generations could also be burdened with morbidity and mortality at the peak of their productivity, potentially affecting the work face and health care systems of various countries across the globe [3].

In India, approximately 75% of T2DM patients have a first-degree family history of T2DM. The lifetime risk of developing the disease is about 40% in offspring of one parent with T2DM and the risk approaches 70% if both parents have diabetes [4].

Asian Indians have a significant familial linkage to diabetes, with a high prevalence of the disease among first-degree relatives and vertical transmission of the disease over two or more generations [5]. Asian Indians have greater insulin resistance compared to Caucasians. As per the "thin fat phenotype" hypothesis, small Indian babies have smaller abdominal viscera and low muscle mass, but more body fat during intrauterine development, which predisposes them to an insulin-resistant state [6].

*Corresponding Author: Kamalakar Mane 0000-0002-8896-321X
E-mail: drkamlakarmane@gmail.com
Phone No.: +91-7972584798

Received on: 26 December 2021
Accepted on: 25 January 2022

The evolution of T2DM is characterized by a defect in insulin secretion (β-cell dysfunction) and insulin action (insulin resistance). Initially, there is an impairment in the body's ability to respond to insulin, which is counterbalanced by compensatory hyperinsulinemia to maintain normal glucose tolerance (NGT). As the fasting blood glucose level keeps on rising, at a certain level, β-cells cannot maintain the elevated rate of insulin secretion, and fasting insulin concentration declines progressively, resulting in impaired glucose tolerance (IGT) and later on T2DM. Progress of NGT to IGT with compensatory hyperinsulinemia is interrelated with the development of insulin resistance (IR). At this stage, it elevated plasma insulin concentrations in post-absorptive and prandial states. Therefore, plasma insulin concentration is widely accepted as a surrogate measure of IR [7]. An early abnormality of insulin secretion and action with a reduction in the first phase of insulin secretion occurs early in the course of disease in first-degree relatives of T2DM patients before glucose tolerance becomes abnormal [8].

First-degree relatives of T2DM who are at high risk for developing T2DM have diminished β-cell function while many of them still have normal glucose tolerance [9]. Insulin resistance predicts the development of T2DM and cardiovascular disease independently of other risk factors [10].

Several alternatives have been proposed to compensate for variations in basal glucose levels, including the use of both fasting glucose and insulin concentrations. One such mathematical model, the Homeostatic Model Assessment of Insulin Resistance Index (HOMA-IR) is widely used. This mathematical concept is based on the hypothesis of a negative feedback loop between the liver and β-cells regulating both fasting glucose and insulin concentrations. It can estimate pancreatic cell function and degree of IR [11]. Insulin resistance is an initial measurable defect in patients who will develop T2DM [12].

$$\text{HOMA} - \text{IR Index} = \frac{\text{Fasting Glucose (mg/dl) x Serum Insulin (μU/ml)}}{405} \quad (1)$$

OR

$$\text{HOMA} - \text{IR Index} = \frac{\text{Fasting Glucose (mmol/L) x Serum Insulin (μU/ml)}}{22.5} \quad (2)$$

Many clinical observations support the role of systemic and/or low-grade chronic inflammation in the pathogenesis of IR. Clinical features of IR and plasma insulin concentrations are correlated with proinflammatory cytokines and acute-phase reactants [13].

It has been proven that β-cell function starts to decline approximately 12 years before the diagnosis of diabetes and genetic susceptibility is the first stage in this process [14]. Hence, we studied subjects with and without a family history of T2DM to explore the impact of family history on insulin resistance. We aimed to detect potential differences in insulin resistance, an inflammatory marker between the groups, and their interrelationship.

2 Material and Methods

The present study was conducted at the Department of Biochemistry, Dr. V.M. Government Medical College, a tertiary care center in Maharashtra, India. Written informed consent was obtained from all the participants. We selected a total of 100 non-diabetic siblings and offspring of T2DM patients between the age group of 20 to 50 years and compared them with 100 healthy controls. The institutional ethical committee approved the research study.

2.1 Inclusion criteria

- Non-diabetic siblings and offspring of T2DM patient.
- Age group: 20 to 50 years.

2.2 Exclusion criteria

- Individuals suffering from T2DM.
- Individuals with impaired glucose tolerance.
- Patients suffering from any acute or chronic cardiovascular disease and any other major illness.
- Patient suffering from acute systemic illness and any inflammatory conditions.
- Subjects taking oral contraceptive pills.

2.3 Relevant indices

- Homeostatic Model Assessment of Insulin Resistance Index (HOMA-IR Index).

2.4 Anthropometry

- Weight (Kg) and Height (meters)
- BMI (kg/m^2): Weight (kg) / Height^2 (meters)
- Normal waist circumference (WC): Male < 85 cm and Female < 80 cm.
- Hip circumference (HC) in cm at the level of greatest protuberance of buttocks without compression of the skin.
- Normal Waist/Hip ratio: Male < 0.89 and Female < 0.81 [1,15].

2.5 Biochemical investigations

12-hour fasting venous blood samples were collected and tested for the following parameters:

- Plasma glucose level: Plasma glucose level was estimated using the glucose oxidase and peroxidase (GOD-POD) method (ERBA Diagnostics, Mannheim, Germany).

- Serum Insulin: Quantitative estimation of serum insulin done by Chemiluminescence Immunoassay (CLIA) using Acculite CLIA microwells kit (Monobind INC., Lake Forest, USA).
- Serum hs-CRP: Quantitative estimation of Serum hs-CRP done by Chemiluminescence Immunoassay (CLIA) using Acculite CLIA microwells kit (Monobind INC., Lake Forest, USA).

2.6 Statistical Analysis

Statistical analysis was performed using IBM SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA). The unpaired t-test was used to compare the mean of the two groups. Pearson's correlation coefficient (r-value) was calculated to determine the association between fasting plasma glucose level, fasting serum insulin, and fasting serum hs-CRP. A *p*-value < 0.05 were considered statistically significant. All data are presented as the means ± SD. To determine the strength of the correlation, positive and negative r values were estimated.

3 Results and Observations

A total of 200 participants were enrolled in this study, of which 100 as cases with a family history of T2DM and 100 as controls without a family history of T2DM. Demographic and biochemical data of the two groups were analyzed as mean ± standard deviation (S.D.). Correlation coefficients (r) between various parameters in cases and controls were calculated.

Table 1 represents the demographic data of the cases and controls. The differences in mean age, weight, and height between cases and controls were not statistically significant. The data showed an increase in mean value of BMI (22.81 ± 1.27 vs. 22.43 ± 1.02, $p < 0.05$) and hip circumference (98.24 ± 6.90 vs. 96.08 ± 5.31, $p < 0.05$) in cases as compared to controls. The data also showed a highly significant difference in mean values of waist circumference (78.98 ± 5.43 vs. 73.97 ± 4.88, $p < 0.001$) and waist/hip ratio (0.81 ± 0.07 vs. 0.77 ± 0.04, $p < 0.001$).

Table 1: Comparison of demographic parameters (Mean ± S.D and *p*-value).

Parameter	Cases (n = 100)	Control (n = 100)	*p*-Value
Age (Years)	35.44 ± 6.18	36.31 ± 5.34	> 0.05
Sex (M/F)	58 / 42	53 / 47	-
Weight (kg)	60.91 ± 7.28	59.93 ± 6.96	> 0.05
Height (m)	1.63 ± 0.08	1.63 ± 0.07	> 0.05
BMI (kg/m²)	22.81 ± 1.27	22.43 ± 1.02	< 0.05
WC (cm)	78.98 ± 5.43	73.97 ± 4.88	< 0.001
HC (cm)	98.24 ± 6.90	96.08 ± 5.31	< 0.05
W/H Ratio	0.81 ± 0.07	0.77 ± 0.04	< 0.001

$p < 0.001$ - highly significant; $p < 0.05$ - Significant

Table 2 shows a comparison of biochemical parameters between cases and controls. The mean value of blood sugar level did not show a significant difference between cases and controls (92.02 ± 9.23 vs. 91.77 ± 7.99, $p > 0.05$). The mean values of insulin (12.52 ± 3.65 vs. 5.08 ± 1.42), HOMA-IR (2.86 ± 0.95 vs. 1.15 ± 0.34), and hs-CRP (2.4 ± 1.98 vs. 1.0 ± 0.38) (all $p < 0.001$) increased in cases as compared to controls.

Table 2: Comparison of biochemical parameters (Mean ± S. D. and *p*-value).

Parameter	Cases (n =100)	Control (n =100)	*p*-Value
BSL 70-110 mg/dl	92.02 ± 9.23	91.77 ± 7.99	> 0.05
Insulin 0.7–9.0 µIU/ml	12.52 ± 3.65	5.08 ± 1.42	< 0.001
HOMA-IR > 2.6	2.86 ± 0.95	1.15 ± 0.34	< 0.001
hs-CRP Up to 1 mg/L	2.4 ± 1.98	1.0 ± 0.38	< 0.001

$p < 0.001$ - highly significant; $p < 0.05$ - Significant

The above data signifies that despite normal fasting blood sugar levels, fasting serum insulin level and HOMA-IR increased in cases.

Statistically significant positive correlation found between serum insulin and hs-CRP levels with waist/ hip ratio (r = 0.4 and 0.19 respectively) than with BMI (r = 0.29 and 0.13 respectively).

Fasting serum insulin shows a positive correlation with HOMA-IR, and hs-CRP ($p < 0.001$). HOMA-IR strongly correlates with hs-CRP and shows a positive correlation ($p < 0.05$) (Fig. 1). Insulin and HOMA-IR shows strong positive correlation with each other (r = 0.94; $p < 0.001$ (Fig. 2).

Table 3: Correlation coefficients (r values) in cases (r-value and *p*-value).

		HOMA-IR	hs-CRP
Insulin	r-value	0.94	0.34
	p-value	< 0.001*	< 0.001*
HOMA-IR	r-value		0.32
	p-value		< 0.05

$p < 0.001$ - highly significant; $p < 0.05$ - Significant

4 Discussion

There is growing evidence supporting the concept that chronic low-grade inflammatory states may have a pathogenic role in IR. Several studies have shown that proinflammatory cytokines and acute-phase reactants correlated with measures of IR, plasma insulin concentration, BMI, and waist circumference. Inflammatory cytokines such as TNF-α and IL-6 are thought to be associated with IR, and their expression is increased in adipose tissue [16].

Serum insulin and hs-CRP levels were found to be strongly correlated with the W/H ratio compared to BMI. Serum insulin strongly correlated with W/H ratio and BMI than hs-CRP. This suggests the role of abdominal obesity on serum insulin and hs-CRP [17].

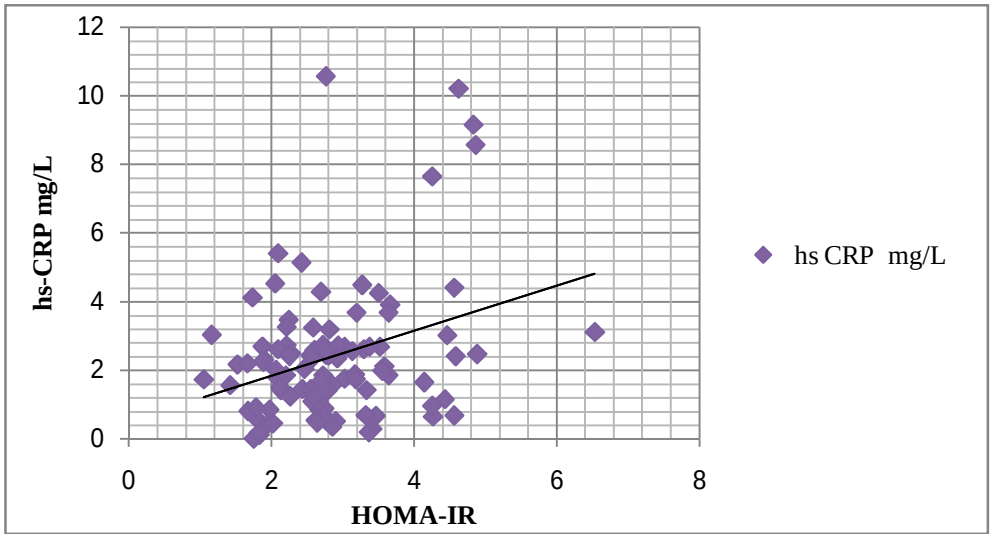

Fig. 1: Graphical correlation of HOMA-IR with hs-CRP.

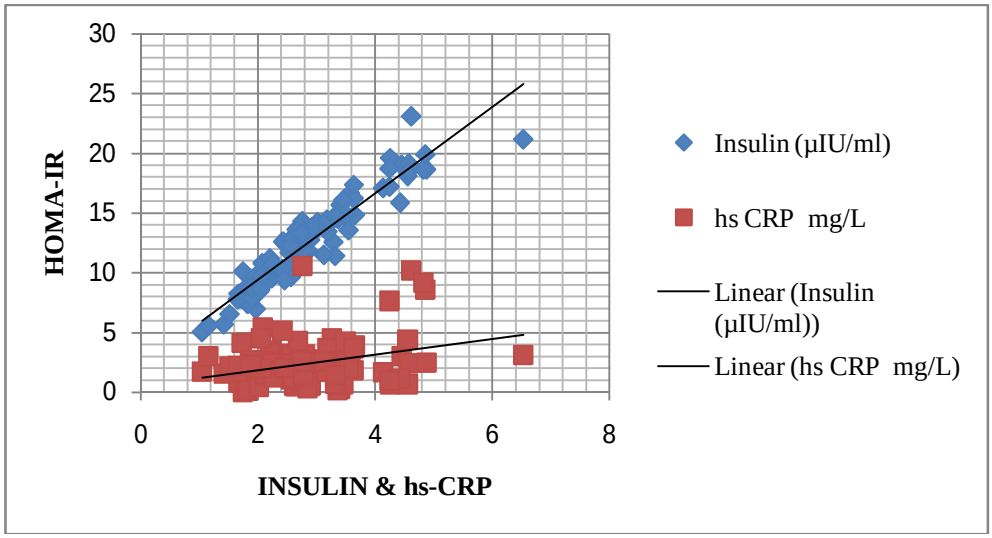

Fig. 2: Graphical correlation of HOMA-IR with insulin and hs-CRP.

Gupta and Jain (2004) concluded that fasting insulin levels significantly correlated with direct estimates of insulin resistance. Fasting insulin is also highly correlated with HOMA [18].

The plausible explanation that could explain the significant correlation of serum insulin and hs-CRP with the W/H ratio is the obvious physical proximity of visceral fat to the portal venous system, metabolites and secretory products such as free fatty acids (FFA) are directly drained into the liver, leading to hepatic IR, which may contribute to enhanced hepatic gluconeogenesis. Since visceral adipocytes are more lipolytically active than subcutaneous adipocytes, visceral fat accumulation may be more harmful than subcutaneous abdominal fat accumulation [19].

Visceral adipocytes produce proinflammatory cytokines like TNF-α, IL-1, IL-6, and specifically secret biologically active peptides such as visfatin and omentin which modulate glucose and lipid metabolism [19]. Increased synthesis of cytokines like IL-6 and TNF-α by visceral adipocytes could contribute to higher hs-CRP production by the liver whenever visceral obesity is evident [20].

Insulin resistance is relatively low in nondiabetic, normotensive obese patients, and is far outweighed by insulin hypersecretion, particularly in women with central obesity. The risk of diabetes, cardiovascular risk, and treatment response may differ among obese people with preserved insulin sensitivity compared to insulin-resistant obesity [21].

Chien-Hsiang *et al.*, (2010) reported that among the 5 anthropometric indices, BMI strongly predicts the incidence of type 2 diabetes. W/H ratio had a significantly adjusted odds ratio and the highest area under the curve to predict the risk of type 2 diabetes [22]. An 11-year follow-up study conducted in 2004 found that

subjects with a high hs-CRP level were 3.6 to 4.1 times more likely to develop diabetes as well as W/H ratio (OR = 1.40, $p = 0.025$), and the log of insulin concentrations (OR = 2.04, $p = 0.025$) were significant baseline predictors of diabetes. Furthermore, no interaction between BMI and hs-CRP was reported [23].

In the present study, we found that level of serum insulin positively correlated with the levels of serum hs-CRP ($r = 0.34$, $p < 0.001$).

Inflammation impairs pancreatic β-cell function in genetically predisposed diabetics. Inflammation could also promote hepatic insulin resistance in individuals who are genetically susceptible to developing diabetes. Fat accumulation in the liver reduced hepatic insulin sensitivity resulting in fasting hyperglycaemia [24].

Gelaye *et al.*, (2010) reported that increased CRP levels were significantly associated with higher mean fasting insulin and mean HOMA-IR concentrations. The findings from that study indicated that women and men with CRP concentration > 2.53 mg/L had a 2.18- and 2.54-fold increased risk of IR respectively [25].

In particular, visceral adipocytes play a key role in regulating inflammation. CRP is synthesized in the liver and regulated by proinflammatory cytokines like interleukin–6 (IL-6) and Tumor Necrosis Factor - α (TNF-α) which lowers the expression of Insulin Receptor Substrate 1 (IRS-1), Glucose Transporter 4 (GLUT-4) and insulin-stimulated glucose transport in first-degree relatives of T2DM patients. This shows that the association between elevated hs-CRP and elevated insulin levels may be related to chronic systemic subclinical inflammation [18]. According to Højbjerre *et al.*, (2011) insulin resistance, and higher plasma C-reactive protein was detected in first-degree relatives of T2DM subjects [26].

Vikram *et al.*, (2006) found a significant correlation of fasting insulin ($r = 0.19$, $p < 0.01$) and hs-CRP ($r = 0.14$, $p < 0.01$) with BMI and hs-CRP levels significantly correlated with ($r = 0.16$, $p < 0.01$) with W/H ratio [27].

We found a positive correlation between HOMA-IR and BMI ($r = 0.31$, $p < 0.005$) and a significant correlation between HOMA-IR and W/H ratio ($r = 0.46$) compared with BMI ($r = 0.31$). The results also revealed a significant correlation of HOMA-IR with BSL ($r = 0.61$) and hs-CRP ($r = 0.32$) as well as a strong correlation of HOMA-IR with insulin ($r = 0.94$, $p < 0.001$) when compared to hs-CRP ($r = 0.32$, $p < 0.05$). These findings suggest the role of insulin and hs-CRP in the development of insulin resistance. Similarly, Kakita *et al.*, (2008) found a positive correlation of HOMA-IR with BMI ($r= 0.365$; $p < 0.001$), Glucose (0.32; $p < 0.001$), Insulin (0.983; $p < 0.001$) [28].

Bahceci *et al.*, (2005) found higher hs-CRP levels ($p=0.0001$) in first-degree relatives of T2DM patients than those without a family history of T2DM. hs-CRP was positively correlated with HOMA-IR ($r = 0.348$; $p<0.02$) [29].

The cut-off point for HOMA-IR from which insulin resistance is detected has been variable in different studies. In our study, patients with a HOMA-IR cut-off point of >2.5 were considered to be insulin-resistant. The cut-off point for defining insulin resistance in men and women is considered based on recently published studies [30]. At this cut-off, we found that 71 first-degree relatives of T2DM subjects were insulin resistant.

The findings of our study are in agreement with previous studies that reported a significantly higher prevalence of impaired fasting glucose, impaired glucose tolerance, and diabetes in first-degree relatives. Furthermore, first-degree relatives had a higher prevalence of insulin resistance as measured by HOMA-IR. The most predominant consequence of insulin resistance is the future development of T2DM. Appreciable β-cell destruction may have already occurred before glucose tolerance or fasting glucose levels become impaired. Thus, efforts to prevent the development of T2DM will be more successful only if intervention is initiated when blood glucose levels are still in the normal range. Interventions such as therapeutic lifestyle changes may be effective in modifying the course of the disease and preventing disease progression [31].

Florez *et al.*, (1995) reported that glycemic and insulin areas were greater ($p < 0.01$) in first-degree relatives of T2DM patients and none of the T2DM relatives have impaired glucose tolerance. The insulin/glucose ratio was also higher ($p < 0.01$) at 120 minutes on OGTT and concludes that this may be an indirect indication of insulin resistance before the development of IGT and diabetes in T2DM relatives [32]. Moreover, insulin resistance, impaired β-cell function, and possibly also adipose tissue dysfunction were found in individuals with a family history of type 2 diabetes and deteriorating glucose tolerance, emphasizing the multifactorial pathophysiology in the development of IGT and T2D [33].

Although, the subjects enrolled in our study were normoglycemic, increased serum insulin and hs-CRP levels suggest that hyperinsulinemia and chronic low-grade inflammation may have an additive and synergistic effect on the development of insulin resistance.

The major strength of our study was the use of two groups of young, healthy subjects with normal glucose tolerance, differing only by the presence or absence of a family history of T2DM. This study design is critical for examining early concomitants of insulin resistance, such as hs-CRP, in the absence of potentially confounding variables such as hyperglycemia. A notable strength of the study was the direct measurement of fasting serum insulin and the estimation of insulin resistance using the HOMA-IR. Although our findings are biologically

plausible, due to the cross-sectional nature of the study, causality cannot be inferred.

5 Conclusion

The key finding of our study was that the normoglycemic first-degree relatives of T2DM had higher fasting serum insulin levels. This suggests that in the first-degree relatives of T2DM subjects, pancreatic β-cell dysfunction may have begun long before the glucose tolerance becomes abnormal. Increased hs-CRP levels in the first-degree relatives of T2DM subjects, indicating that insulin resistance is a state of chronic low-grade systemic inflammation. Therefore, we suggest screening genetically predisposed first-degree relatives of T2DM patients. Timely screening and early detection of insulin resistance in first-degree relatives of T2DM patients may allow clinicians to act early in the disease's course and prevent future complications and consequences.

Acknowledgment

We would like to thank all the health care workers who volunteered for this study.

Conflict of interest

The authors declare no conflict of interest.

References

[1]. Ramachandran, A. & Snehalatha, C. (2009). Current scenario of diabetes in India. *J. Diabetes*, *1*(1): 18–28. https://doi.org/10.1111/j.1753-0407.2008.00004.x.

[2]. Mohan, V., Sandeep, S., Deepa, R., Shah, B. & Varghese, C. (2007). Epidemiology of type 2 diabetes: Indian scenario. *Indian J. Med. Res.*, *125*(3): 217–230.

[3]. Alberti, G., Zimmet, P., Shaw, J., Bloomgarden, Z., Kaufman, F. & Silink, M. (2004). Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. *Diabetes Care*, *27*(7): 1798–1811. https://doi.org/10.2337/diacare.27.7.1798.

[4]. Ridderstråle, M. & Groop, L. (2009). Genetic dissection of type 2 diabetes. *Mol. Cell. Endocrinol.*, *297*(1-2): 10–17. https://doi.org/10.1016/j.mce.2008.10.002.

[5]. Jali, M.V. & Kambar, S. (2006). Prevalence of diabetes amongst the family members of known diabetics. *Int. J. Diab. Dev. Ctries.*, *26*(2): 81-85.

[6]. Mohan, V. (2004). Why are Indians more prone to diabetes? *J. Assoc. Physicians India*, 52: 468–474.

[7]. Kashyap, S.R. & Defronzo, R.A. (2007). The insulin resistance syndrome: physiological considerations. *Diab. Vasc. Dis. Res.*, *4*(1): 13–19. https://doi.org/10.3132/dvdr.2007.001.

[8]. Guillausseau, P.J., Meas, T., Virally, M., Laloi-Michelin, M., Médeau, V. & Kevorkian, J.P. (2008). Abnormalities in insulin secretion in type 2 diabetes mellitus. *Diabetes Metab.*, *34*: S43–S48. https://doi.org/10.1016/S1262-3636(08)73394-9.

[9]. Kahn, S.E. (2001). The Importance of β-Cell Failure in the Development and Progression of Type 2 Diabetes. *J. Clin. Endocrinol. Metab.*, *86*(9): 4047–4058. https://doi.org/10.1210/jcem.86.9.7713.

[10]. Ruotsalainen, E., Stančáková, A., Vauhkonen, I., Salmenniemi, U., Pihlajamäki, J., Punnonen, K. & Laakso, M. (2010). Changes in Cytokine Levels During Acute Hyperinsulinemia in Offspring of Type 2 Diabetic Subjects. *Atherosclerosis*, *210*(2): 536–541. https://doi.org/10.1016/j.atherosclerosis.2009.11.036.

[11]. Ferrara, C.M. & Goldberg, A.P. (2001). Limited Value of the Homeostasis Model Assessment to Predict Insulin Resistance in Older Men with Impaired Glucose Tolerance. *Diabetes Care*, *24*(2): 245–249. https://doi.org/10.2337/diacare.24.2.245.

[12]. Czech, M.P. (2017). Insulin action and resistance in obesity and type 2 diabetes. *Nat. Med.*, *23*: 804–814. https://doi.org/10.1038/nm.4350.

[13]. Rehman, K. & Akash, M.S. (2016). Mechanisms of inflammatory responses and development of insulin resistance: how are they interlinked? *J. Biomed. Sci.*, *23*(1): 87. https://doi.org/10.1186/s12929-016-0303-y.

[14]. Eriksson, J., Lindström, J. & Tuomilehto, J. (2001). Potential for the prevention of type 2 diabetes. *Br. Med. Bull.*, *60*(1): 183–199. https://doi.org/10.1093/bmb/60.1.183.

[15]. Mehta, S.R., Kashyap, A.S. & Das, S. (2009). Diabetes Mellitus in India: The Modern Scourge. *Med. J. Armed Forces India*, *65*(1): 50–54. https://doi.org/10.1016/S0377-1237(09)80056-7.

[16]. Hossain, M., Faruque, M.O., Kabir, G., Hassan, N., Sikdar, D., Nahar, Q. & Ali, L. (2010). Association of serum TNF-α and IL-6 with insulin secretion and insulin resistance in IFG and IGT subjects in a Bangladeshi population. *Int. J. Diabetes Mellit.*, *2*(3): 165–168. https://doi.org/10.1016/j.ijdm.2010.08.004.

[17]. Song, Y., Yang, S.K., Kim, J. & Lee, D.C. (2019). Association between C-Reactive Protein and Metabolic Syndrome in Korean Adults. *Korean J.*

Fam. Med., *40*(2): 116–123. https://doi.org/10.4082/kjfm.17.0075.

[18]. Gupta, A.K. & Jain, S.K. (2004). A study to evaluate surrogate markers of insulin resistance in forty euglycemic healthy subjects. *J. Assoc. Physicians India*, *52*: 549–553.

[19]. Sandeep, S., Gokulakrishnan, K., Velmurugan, K., Deepa, M. & Mohan, V. (2010). Visceral & subcutaneous abdominal fat in relation to insulin resistance & metabolic syndrome in non-diabetic south Indians. *Indian J. Med. Res.*, *131*: 629–635.

[20]. Ellulu, M.S., Patimah, I., Khaza'ai, H., Rahmat, A. & Abed, Y. (2017). Obesity and inflammation: the linking mechanism and the complications. *Arch. Med. Sci.*, *13*(4): 851–863. https://doi.org/10.5114/aoms.2016.58928.

[21]. Ferrannini, E., Natali, A., Bell, P., Cavallo-Perin, P., Lalic, N. & Mingrone, G. (1997). Insulin resistance and hypersecretion in obesity. *J. Clin. Invest.*, *100*(5): 1166–1173. https://doi.org/10.1172/JCI119628.

[22]. Cheng, C.H., Ho, C.C., Yang, C.F., Huang, Y.C., Lai, C.H. & Liaw, Y.P. (2010). Waist-to-hip ratio is a better anthropometric index than body mass index for predicting the risk of type 2 diabetes in Taiwanese population. *Nutr. Res.*, *30*(9): 585–593. https://doi.org/10.1016/j.nutres.2010.08.007.

[23]. Laaksonen, D.E., Niskanen, L., Nyyssönen, K., Punnonen, K., Tuomainen, T.P., Valkonen, V.P., Salonen, R. & Salonen, J.T. (2004). C-reactive protein and the development of the metabolic syndrome and diabetes in middle-aged men. *Diabetologia*, *47*(8): 1403–1410. https://doi.org/10.1007/s00125-004-1472-x.

[24]. Tsalamandris, S., Antonopoulos, A.S., Oikonomou, E., Papamikroulis, G.A., Vogiatzi, G., Papaioannou, S., Deftereos, S. & Tousoulis, D. (2019). The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *Eur. Cardiol.*, *14*(1): 50–59. https://doi.org/10.15420/ecr.2018.33.1.

[25]. Gelaye, B., Revilla, L., Lopez, T., Suarez, L., Sanchez, S.E., Hevner, K., Fitzpatrick, A.L. & Williams, M.A. (2010). Association between insulin resistance and c-reactive protein among Peruvian adults. *Diabetol. Metab. Syndr.*, *2*: 30. https://doi.org/10.1186/1758-5996-2-30.

[26]. Højbjerre, L., Sonne, M.P., Alibegovic, A.C., Nielsen, N.B., Dela, F., Vaag, A., Bruun, J.M. & Stallknecht, B. (2011). Impact of Physical Inactivity on Adipose Tissue Low-Grade Inflammation in First-Degree Relatives of Type 2 Diabetic Patients. *Diabetes Care*, *34*(10): 2265–2272. https://doi.org/10.2337/dc11-0631.

[27]. Vikram, N.K., Misra, A., Pandey, R.M., Dwivedi, M., Luthra, K., Dhingra, V. & Talwar, K.K. (2006). Association between subclinical inflammation & fasting insulin in urban young adult North Indian males. *Indian J. Med. Res.*, *124*(6): 677–682.

[28]. Kakita, A., Suzuki, A., Nagata, M. & Itoh, M. (2008). Association of insulin resistance indexes QUICKI and HOMA-IR with the parameters of metabolic syndrome in non-diabetes Japanese male population. *Anti-Aging Med.*, *5*(8): 82–86. https://doi.org/10.3793/jaam.5.82

[29]. Bahceci, M., Tuzcu, A., Ogun, C., Canoruc, N., Iltimur, K. & Aslan, C. (2005). Is serum C-reactive protein concentration correlated with HbA1c and insulin resistance in Type 2 diabetic men with or without coronary heart disease? *J. Endocrinol. Invest.*, *28*(4): 145–150. https://doi.org/10.1007/BF03345357.

[30]. Keskin, M., Kurtoglu, S., Kendirci, M., Atabek, M.E. & Yazici, C. (2005). Homeostasis Model Assessment Is More Reliable Than the Fasting Glucose/Insulin Ratio and Quantitative Insulin Sensitivity Check Index for Assessing Insulin Resistance Among Obese Children and Adolescents. *Pediatrics*, *115*(4): e500–e503. https://doi.org/10.1542/peds.2004-1921.

[31]. Kumar, A., Tewari, P., Sahoo, S.S. & Srivastava, A.K. (2005). Prevalence of insulin resistance in first degree relatives of type-2 diabetes mellitus patients: A prospective study in north Indian population. *Indian J. Clin. Biochem.*, *20*(2): 10–17. https://doi.org/10.1007/BF02867394.

[32]. Florez, H., Valbuena, H., Ryder, E., Rincón, E., Campos, G., Castillo, S., González, J., Fernández, V., Raleigh, X. & Gómez, M.E. (1995). Dislipidemias e hiperinsulinemia en familiares normoglicémicos- obesos de pacientes con diabetes mellitus no insulinodependiente [Dyslipidemia and hyperinsulinemia in normoglycemic-obese relatives of patients with non-insulin dependent diabetes mellitus]. *Invest. Clin.*, *36*(3): 131–147.

[33]. Henninger, J., Hammarstedt, A., Rawshani, A. & Eliasson, B. (2015). Metabolic predictors of impaired glucose tolerance and type 2 diabetes in a predisposed population – A prospective cohort study. *BMC Endocr. Disord.*, *15*: 51. https://doi.org/10.1186/s12902-015-0048-8.