Original Article

# The relationship among Insulin resistance and Carbohydrate antigen CA 19-9 in Iraqi subjects with type 2 Diabetes mellitus

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## Abstract

Background: Insulin resistance is a common occurrence in a variety of metabolic disorders, including metabolic syndrome (MetS) and Type 2Diabetes Mellitus (T2DM) which is a major medical problem worldwide and can be qualified as the last stage of chronic pancreatitis. As a result, the measurement of insulin resistance is required to determine the relationship between them.

Objectives:- This study is an attempt to investigate the relationship between insulin resistance and the Carbohydrate antigen CA19-9 level in type 2 diabetes mellitus patients.

Methods:- Type 2Diabetes Mellitus (T2DM) has been considered in this search. The average age of patients is (46.56±1.10) years and the average duration of the disease is (6.6±0.94) years divided into two groups. Group I, consisting of forty patients who have type 2 diabetes mellitus with a high level of CA19-9. Group II consisted of forty patients who have normal CA19-9 levels. Forty healthy individuals with a mean age of (44.7±1.45) years were classified as a control group. Fasting blood sugar is measured in the serum of patients, glycated hemoglobin is measured in the whole blood of patients, CA19-9 and total insulin levels were measured in serum by ELISA technique.

Results:- The mean ± SE serum level of CA19-9 in patients with T2DM in groups I and II are (49.933±2.004)U/ml; (16.378±0.6560)U/ml respectively were significantly higher than the mean±SE serum level in the control group (5.683±1.069)U/ml. While the mean±SE serum level of HOMA-IR for the same patients in groups I and II are (10.149±1.0206) and (4.005±0.5221) respectively were significantly higher than the mean±SE serum level in the control group (1.058±0.097).

Conclusion:- The blood levels of CA19-9 and HOMA-IR are positively correlated in patients with T2DM

**Keywords:** Diabetes mellitus type 2, Insulin resistance, Level of CA19-9.

## Introduction

90–95 percent of diabetics worldwide have type 2 diabetes mellitus, is a severe medical issue with significant economic implications. In the previous 30 years, the disease's prevalence has increased [1, 2, 3, 4, 5, 6]. Type 2 diabetes, also known as non-insulin-dependent diabetes mellitus (NIDDM), affects people in middle age or older and who are also overweight or obese.

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It can also affect obese adolescents, and it is more common in women with a history of gestational diabetes and people with dyslipidemia or hypertension. With age, lack of physical activity, and obesity, the risk of developing this kind increases. [7, 8, 9, 10]

75–85% of persons with type 2 diabetes have obesity, dyslipidemia, insulin resistance, or hyperinsulinemia before they are diagnosed with T2DM. [11, 12, 13].

The synthesis of insulin remains steady in this type, but the fundamental issue is a two-fold defect: impaired β-cell function (insulin secretion) and reduced insulin action. Impaired insulin action, i.e. insulin resistance, occurs when target tissues are unable to respond to normal insulin concentrations. In order to sustain euglycemia, β-cells in the pancreas must increase insulin output. Over time, the functional deficiency in insulin secretion prevents the β-cell from maintaining its high insulin secretion rate. As a result, glucose tolerance is harmed, and type 2 diabetes develops.[14, 15, 16, 17].

CA 19-9 is a carbohydrate antigen that has been used to diagnose a variety of cancers, including pancreatic cancer, cancer of the upper gastrointestinal tract, hepatocellular cancer, liver cancer, colorectal cancer, and ovarian cancer. Additionally, it serves as a marker for the effects of diabetes on pancreatic tissue. [18, 19, 20, 21].

Insulin resistance, which is defined as a diminished physiological response of peripheral tissues to the action of normal levels of insulin, is a common finding in metabolic disorders such as metabolic syndrome (MetS) and type 2 diabetes.[22] To investigate the relationship between insulin resistance and MetS, a reliable measure of insulin resistance is required. Identifying those who have insulin resistance is also a method for identifying high-risk patients who can benefit from targeted preventive treatments because insulin resistance is a substantial risk factor for the emergence of type 2 diabetes and the development of cardiovascular disease.[23, 24, 25]

## Methods:-

Eighty patients with type 2 diabetes mellitus were separated into two groups: one with a standard error of mean age of 46.5625 1.1054 years and the other with a standard error of mean duration of 6.6 0.9421. A high amount of CA19-9 was seen in Group I, which included forty patients with type 2 diabetes mellitus. A total of forty patients in Group II had normal CA19-9 values. The control group consisted of forty healthy individuals with a standard error of mean age of 44.7±1.45 years. From October 2021 to February 2022, blood samples were taken from all 120 subjects at Al-Imamain Al-Kadhimain Medical City in Baghdad, Iraq. The Al-Nahrain University/College of Medicine Research Ethics Committee has given their clearance.

Patients with any type of cancer, as well as those with a history of pancreatic, thyroid, hepatic, or renal disease, pregnant women, and smokers, were excluded.

After centrifuging blood samples at 3000 rpm, the serum was stored at -20oC. Fasting blood sugar was assessed using an enzymatic colorimetric method (Chemistry Analyzer), and serum CA 19-9 and total insulin levels were evaluated using a monoclonal antibody Enzyme-Linked Immunosorbent Assay (ELISA) approach. Using the NycoCard reading equipment, whole blood was utilized to determine glycated hemoglobin (HbA1c).

The standard error of the mean is used to display the results of the laboratory test (SEM). The means of the several groups were compared using the Student's t-test.

Microsoft Excel 2013 and SPSS version 20 were used for all other analyses (Statistical Package for Social Sciences). A statistically significant p-value was defined as one that was less than or equal to 0.05.

## Results:-

The level of fasting blood sugar of the studied individuals was summarized in table (1). FBS levels were significantly higher in the T2DM patient's groups compared with the controls ($p < 0.05$).

Table (1):- summary of FBS (mmol\L) level

| Parameter | Group I (N = 40) | Control (N = 40) | Group II (N = 40) | Control (N = 40) |
|---|---|---|---|---|
| **Mean ± SE** | 10.454 ± 0.530 | 4.926 ± 0.054 | 11.53 ± 0.762 | 4.926 ± 0.054 |
| **Median (Range)** | 10.639 (5.722 - 18.889) | 4.944 (4.444 -5.444) | 11 (5.556 - 20.889) | 4.944 (4.444 -5.444) |
| **P value** | <0.001 | | <0.001 | |

While there is no significant difference had been observed between the two diabetic groups (p = 0.593).

The glycated hemoglobin level of the studied individuals was summarized in table (2). In comparison to the controls, HbA1c values were considerably higher in the T2DM patient groups (p 0.05).

Table (2):- summary of HbA1c % level

| Parameter | Group I (N = 40) | Control (N = 40) | Group II (N = 40) | Control (N = 40) |
|---|---|---|---|---|
| **Mean ± SE** | 9.203 ± 0.333 | 5.863 ± 0.078 | 9.058 ± 0.270 | 5.863 ± 0.078 |
| **Median (Range)** | 8.95 (6.7-15.5) | 6 (4.6-6.5) | 8.7 (6.6-13) | 6 (4.6-6.5) |
| **P value** | <0.001 | | <0.001 | |

A significant difference had been observed between the two diabetic groups (p = 0.029).

Homeostatic model assessment of insulin resistance level of the studied individuals was summarized in table (3) which is calculated by dividing the result of fasting plasma glucose (FPG) by fasting plasma insulin (FPI), then multiplying the result by 22.5 as the following equation:

$$HOMA\text{-}IR = (FPG*FPI) / 22.5$$

HOMA-IR levels were significantly higher in the T2DM patient's groups compared with the controls (p < 0.05).

Table (3):- summary of HOMA-IR

| Parameter | Group I (N = 40) | Control (N = 40) | Group II (N = 40) | Control (N = 40) |
|---|---|---|---|---|
| **Mean ± SE** | 10.149 ± 1.021 | 1.058 ± 0.097 | 4.657± 0.884 | 1.058 ± 0.097 |
| **Median (Range)** | 8.976 (3.253- 32.447) | 0.970 (0.227-2.294) | 3.102 (2.462-27.026) | 0.970 (0.227-2.294) |
| **P value** | <0.001 | | <0.001 | |

Table (4) provides a summary of the individuals' serum CA19-9 concentrations. In comparison to the controls, serum CA19-9 levels were substantially higher in the T2DM patient groups (p 0.05).

Table (4):- summary of CA19-9 (U\ml) level

| Parameter | Group I (N = 40) | Control (N = 40) | Group II (N = 40) | Control (N = 40) |
|---|---|---|---|---|
| **Mean ± SE** | 49.9334 ± 2.004 | 6.433 ± 1.309 | 16.378 ± 0.656 | 6.433 ± 1.309 |
| **Median (Range)** | 47.7965 (37.373-99.568) | 1.68 (0.001-28.965) | 15.478 (10-24.001) | 1.68 (0.001-28.965) |

| | | |
|---|---|---|
| **P value** | <0.001 | <0.001 |

## Discussion:-

The health of millions of people is impacted by the global epidemic of diabetes mellitus. The autoimmune destruction of insulin-producing beta cells in the pancreas is a defining feature of type 1 diabetes, whereas insulin resistance and abnormalities in beta-cell insulin secretion are the combined causes of type 2 diabetes.[26]

CA 19-9 is a carbohydrate antigen that is used to diagnose pancreatic cancer as well as pancreatic tissue damage caused by diabetes. As a result, the degree of rising in the CA19-9 level may be useful in distinguishing between pancreatic inflammatory disorders and pancreatic cancer. Therefore, to avoid the necessity for extra interventional procedures, the normal range for diabetic patients must be established before the analysis of CA19-9 levels in these patients. [27,29]

The results of the present investigation showed that serum CA19-9 levels were considerably higher in patients with type 2 diabetes mellitus.

Furthermore, there is no discernible difference (in CA19-9 level) between patients who are receiving treatment (with a standard error of mean duration (mean± SEA) (6.6 0.94) years and those who are not receiving treatment (newly diagnosed patients), which is consistent with Benhamou et al. They came to the conclusion that in diabetes patients, CA 19-9 levels are higher in acute metabolic circumstances, and that this correlates well with blood glucose levels. [27]

Matthews et al. established the homeostasis model assessment estimated insulin resistance (HOMA-IR), which is commonly employed in studies to measure insulin resistance. Quantification of insulin resistance with HOMA-IR is more convenient than the "gold" standard euglycemic clamp method [30, 31], is calculated by dividing the result of fasting plasma glucose (FPG) by fasting plasma insulin (FPI), then multiplying the result by 22.5 as the following equation. [32]

$$\text{HOMA-IR} = (\text{FPG}*\text{FPI}) / 22.5$$

The pathophysiological foundations for the impairment of glucose metabolism and type 2 diabetes are impaired β-cell function and insulin resistance.

Patients with type 2 diabetes mellitus have a considerably higher blood HOMA-IR level than those in the control group, according to the findings of this study.

Furthermore, there is a clear distinction between patients who are receiving treatment (with a standard error of mean duration (mean SEA) of 6.6 0.94 years) and those who are not receiving treatment (with a standard error of mean duration (mean SEA) of 6.6 0.9421 years) and those who are not receiving treatment (newly diagnosed patients).

This finding is consistent with the findings of the White Hall II population-based prospective study, which found that abnormal glucose tolerance occurred (3–5) years after insulin sensitivity had decreased significantly, while pancreatic-cell (which secreted the insulin hormone) function remained unchanged during this time, implying that insulin resistance may be a determining factor in the transition from normal glucose tolerance to prediabetes.[33,34] This explains why there is no discernible difference in CA19-9 levels between patients who are receiving treatment (with a standard error of mean duration (mean SEA) of 6.6 ± 0.94 years) and those who are not (newly diagnosed patients).

## Conclusion

There is a clear direct relationship between the level of carbohydrate antigen CA19-9 and HOMA-IR in patients with type 2 diabetes, which indicates the possibility of damage to pancreatic tissue in people with insulin resistance.

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Author contribution

Dr. Hassan H. AL-Saeed suggests the study; Dr. Mahmood Shakir Khudhair select the suitable patients and both of them co-writes the manuscript for the study and Miss Russul R. AL-Hamaoy collected the blood samples, conducted the necessary analysis of the study, writes the paper, and analyzed the results statistically.

Conflict of interest: - There was no conflict of interest.

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## References

[1] Makki Maha J. A., Jawad Abdullah M. and Umran Hussam J., The potential therapeutic benefit of paracetamol in treatment of patients with type-2 diabetes mellitus; the medical journal of basrah university, 2013, Vol. 31, pp. 47- 52.
[2] Wild S. et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030; Diabetes Care, 2004, Vol. 27, pp. 1047–1053.
[3] Rokhsareh Aghili, Mojtaba Malek, Ameneh Ebrahim Valojerdi, Zahra Banazadeh, Laily Najafi, Body composition in adults with newly diagnosed type 2 diabetes: effects of metformin; Journal of Diabetes & Metabolic Disorders, 2014, vol. 13, pp. 2-8.
[4] Waqas M, Idrees M, Qayyum S, Ihtesham M, Shafi M, Rahman IU. METFORMIN MODULATES SERUM CA 19-9 AND ITS RELATED FACTORS MORE EFFECTIVELY THAN GLIBENCLAMIDE IN DIABETIC PATIENTS. JMS [Internet]. 2022 Sep. 30 [cited 2022 Oct.

16];30(3):212-5. Available from:
[5] Salman K. Ajlan, Abdulkader A. Abdulkader & Asaeer Y. Mijbil, The impact of metabolic syndrome in type 2 diabetic patients; The Medical Journal of Basrah University, 2012, vol. 30, pp. 85-90.
[6] Parker N. Hyde, Teryn N. Sapper, Christopher D. Crabtree, Richard A. LaFountain, Madison L. Bowling, Alex Buga, Brandon Fell, Fionn T. McSwiney, Ryan M. Dickerson, Vincent J. Miller, Debbie Scandling, Orlando P. Simonetti, Stephen D. Phinney, William J. Kraemer, Sarah A. King, Ronald M. Krauss, and Jeff S. Volek. Dietary carbohydrate restriction improves metabolic syndrome independent of weight loss; JCI insight, 2019, vol.4 (12).
[7] Silvio E. Inzucchi,1 Richard M. Bergenstal, John B. Buse, Michaela Diamant, Ele Ferrannini, Michael Nauck,Anne L. Peters, Apostolos Tsapas, Richard Wender and David R. Matthews. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach; Diabetes Care, January 2015, vol. 38, pp. 140-149.
[8] C.L. Hanis , E. Boerwinkle , R. Chakraborty, D.L. Ellsworth , P. Concannon, B. Stirling, V.A. Morrison , B. Wapelhorst , R.S. Spielman, K.J. Gogolin-Ewens , J.M. Shephard, S.R. Williams, N. Risch\ D. Hinds, N. lwasaki, M. Ogata, Y. Omori. A genome-wide search for human non¬insulin-dependent (type 2) diabetes genes reveals a major susceptibility locus on chromosome 2; Nature Publishing Group, June 1996, vol. 13, pp.161-166.
[9] Salim M.,Alruba'ae, None anticipated bacterial urinary tract infections in type 2 diabetic patients relative to duration and angiopathies; Al – Kindy Col Med J, 2011, vol. 7, pp. 37-44.
[10] American Diabetes Association, Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes; Diabetes Care 2019 Jan; 42, pp. S13-S28.
[11] O'Neill S, O'Driscoll L. Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. Obesity reviews. 2015 Jan;16(1):1-2.
[12] Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Annals of internal medicine. 1990 Dec 15;113(12):909-15.
[13] Davidson MB. Correction to the Bergman review. Diabetes research and clinical practice. 2021 Oct 1;180.
[14] Ryu TY, Park J, Scherer PE. Hyperglycemia as a risk factor for cancer progression. Diabetes & metabolism journal. 2014 Oct 1;38(5):330-6.
[15] Francesca Cirillo, Cecilia Catellani, Chiara Sartori, Pietro Lazzeroni, Sergio Amarri and Maria Elisabeth Street, Obesity, Insulin Resistance, and Colorectal Cancer: Could miRNA Dysregulation Play a Role?; Int. J. Mol. Sci. 2019, 20(12)
[16] Wongwananuruk T, Rattanachaiyanont M, Indhavivadhana S, Leerasiri P, Techatraisak K, Tanmahasamut P, Angsuwathana S, Dangrat C. Prevalence and clinical predictors of insulin resistance in reproductive-aged thai women with polycystic ovary syndrome. International Journal of Endocrinology. 2012 Jan 1;2012.
[17] RochelleDavis, Maxine P.Bonham, Kay Nguo and Catherine E.Huggins, Glycaemic response at night is improved after eating a high protein meal compared with a standard meal: A cross-over study; Clinical Nutrition, 2019, vol 38.
[18] Al-Hamaoy RR, Al-Saeed HH, Khudhair MS. Determination of carbohydrate antigen 19-9 level in Sera of Iraqi patients with type 2 diabetes mellitus. Mustansiriya Medical Journal. 2019 Jan 1;18(1):20.
[19] Felix Rückert, Christian Pilarsky and Robert Grützmann, Serum Tumor Markers in Pancreatic Cancer—Recent Discoveries; Cancers, 2010, pp.1107-1124.
[20] Harmenberg U, Wahren B, Wiechel KL., Tumor markers carbohydrate antigens CA 19-9 and CA 50 and Carcinoembryonic antigen in pancreatic cancer and benign diseases of the pancreatobiliary tract; Cancer Research,1988.
[21] Azizian Azadeh; Rühlmann Felix; Krause, Tanja; Bernhardt, Markus; Jo, Peter; et al. CA19-9 for detecting recurrence of pancreatic cancer; Scientific Reports (Nature Publisher Group); London 2020, Vol. 10, Iss.1.
[22] Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, and Kahn CR., Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study; Lancet, 1992, 340: 925-929.
[23] Hanley AJ, Williams K, Stern MP, Haffner SM., Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study; Diabetes Care 2002, 25:1177-1184.
[24] Rutter MK, Meigs JB., Sullivan LM., D'Agostino RB Sr., Wilson PW., Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study; Diabetes, 2005, 54:3252-3257.
[25] Alireza Esteghamati, Haleh Ashraf, Omid Khalilzadeh, Ali Zandieh, Manouchehr Nakhjavani, Armin Rashidi, Mehrdad Haghazali, Fereshteh Asgari, Optimal cut-off of homeostasis model assessment of insulin resistance (HOMA-IR) for the diagnosis of metabolic syndrome: third national surveillance of risk factors of noncommunicable diseases in Iran (SuRFNCD-2007); Nutrition & Metabolism, 2010.
[26] Jomana Khawandanah, Double or hybrid diabetes; A systematic review on disease prevalence, characteristics and risk factors; Nutrition & Diabetes ,2019, 9;33.
[27] Benhamou P.Y. et al. Influence of metabolic disturbances of diabetes mellitus on serum CA 19-9 tumor marker; Diabete Metab, 1991,Vol. 17, pp. 39-43.
[28] Si-Biao Su, Shan-Yu Qin, Wen Chen, Wei Luo, and Hai-Xing Jiang; Carbohydrate antigen 19-9 for differential diagnosis of pancreatic carcinoma and chronic pancreatitis. World J Gastroenterol, 2015, 21(14): 4323–4333.
[29] Kamile Gul MD, Sevinc Nas MD, Didem Ozdemir MD,Reyhan Ersoy MD,Bekir Cakir MD, Mehmet Gumus MD; CA19-9 level in patients with type 2 Diabetes Mellitus and Its Relation to the Metabolic Control and Microvasclar complications; The American Journal of the Medical Sciences, 2011, 341, p28-32.
[30] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and b-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412–419.
[31] Kim HR, Lee CH, Kim YW, Han SK, Shim YS, Yim JJ. Increased CA 19-9 level in patients without malignant disease. Clinical chemistry and laboratory medicine. 2009 Jun 1;47(6):750-4.
[32] Hui-Qi Qu1, Quan Li2, Anne R. Rentfro3, Susan P. Fisher-Hoch1, Joseph B. McCormick (2011) The Definition of Insulin Resistance Using HOMA-IR for Americans of Mexican Descent Using Machine Learning. PLoS ONE 6(6): e21041.
[33] Kanaya AM, Herrington D, Vittinghof E, et al. Understanding the high prevalence of diabetes in US south Asians compared with four racial/ethnic groups: the MASALA and MESA studies. Diabetes Care. 2014;37:1621–8.
[34] Hulman A, Simmons RK, Brunner EJ, et al. Trajectories of glycaemia, insulin sensitivity and insulin secretion in South Asian and white individuals before diagnosis of type 2 diabetes: a longitudinal analysis from the Whitehall II cohort study. Diabetologia. 2017;60:1252–60.