Is there exocrine pancreatic dysfunction in insulin resistance?

ABSTRACT

Introduction: The aim of our study is to determine whether insulin resistance has any effect on pancreatic exocrine function in people with insulin resistance.

Method: The study included 43 insulin resistant cases with HOMA-IR≥2.5 and 43 controls (HOMA-IR <2.5.) without any disease, pregnancy. Body mass indices of all participants were calculated. Fasting blood glucose, insulin, HbA1c, total cholesterol, triglyceride, HDL, LDL, creatinine, ALT, AST, Adiponectin, Leptin, pancreatic amylase, lipase were studied in both groups.

Results: The insulin resistance (IR) group consisted of 38 women 5 men and the control group 33 women 10 men. Statistically, both groups were similar in respect to gender and age (p: 0.25, 0.11, respectively). While the lowest and highest BMI in the IR group was 20.58-44, these values were 18.7-37.3 in the controls and were significantly higher in the case group (p 0.00). Fecal Elastase-1 levels were significantly lower in the IR group (p: 0.00). Blood glucose, insulin and HbA1c levels were significantly higher in the IR group than in the control (p: 0.00, 0.00, 0.00, respectively). Leptin levels were significantly higher in the IR group compared to the controls (p: 0.01).

In the Pearson correlation analysis in the group with insulin resistance, a significant positive relation (p: 0.022 r: +0.34) was detected between HOMA-IR and Adiponectin. There was a significant negative relation between pancreatic amylase and HOMA-IR (p: 0.029, r: -0.33), a significant negative relation between Fecal Elastase-1 and Adiponectin (p: 0.038, r: -0.31), a significant positive relation between Leptin and Adiponectin (p : 0.00, r: 0.59).

Conclusion: Fecal Elastase -1 level decreased markedly in patients with insulin resistance, showing pancreatic exocrine dysfunction.

Keywords: Pancreatic exocrine dysfunction, Fecal Elastase 1, Insulin resistance*

Introduction

Exocrine pancreatic insufficiency is a condition that occurs due to insufficient release or activity of pancreatic digestive enzymes, especially pancreatic lipase.[1] There are studies reporting that Fecal elastase-1, an indirect test, is extremely sensitive in the diagnosis of severe and moderate exocrine pancreatic insufficiency and has a significantly higher sensitivity than faecal chymotrypsia.[2] Detection of FE-1 level below 200 mcg / g is an indicator of pancreatic exocrine dysfunction.[3]

Islet tissue, which is the endocrine part of the pancreas, is in close contact with exocrine cells anatomically and physiologically. Insulin produced by beta cells has a trophic effect on

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exocrine acini. Microvascular damage can induce pancreatic fibrosis and decrease pancreatic volume in diabetic patients.[4] Low Fecal Elastase-1 (FE-1) levels, which indicate exocrine disruption in relation to insulin requirement, poor glycemic control, and long disease period, were detected as 12-73% in type 2 diabetic patients.[5]

Progressive beta cell damage in the presence of insulin resistance is a feature of type 2 diabetes.[6] There is a clear relationship between insulin resistance, obesity and type 2 Diabetes Mellitus. Most of the type 2 DM patients have insulin resistance.[7] Adiponectin, an adipokine released by adipose tissue, decreases in insulin resistance. An increased level of Leptine, which is also an adipokine, is directly related to obesity. [8] [9] [10]

The aim of our study is to determine whether insulin resistance has any effect on pancreatic exocrine function in people with insulin resistance at the stage before diabetes occurred.

Material and Methods

Ethical approval for our study was obtained from Van Yuzuncu Yil University ethics committee and an informed consent form was signed by all participants. Our study is a prospective and cross-sectional study. 43 patients, aged between 18-68 years, who were diagnosed with insulin resistance between 15/3/2018 and 15/3/19 at the Yuzuncu Yil University Medical Faculty Internal Medicine Policlinic were included in our study. As the control group, 43 people, aged 19-68, who did not have a chronic disease or pregnancy and applied to the Internal Medicine Outpatient Clinic and who did not have any abnormalities in physical examination and laboratory tests, were included in the study.

The criteria for exclusion are under the age of 18, over 70, steatore, pancreatic-biliary obstruction, history of alcohol-smoking, kidney failure, pregnancy, chronic or serious concomitant diseases, diabetes mellitus. Whether patients had pancreatitis was questioned verbally, those with such a history were excluded from the study.

After 10 hours of fasting, blood samples were taken to study adiponectin, leptin, glucose, insulin, pancreatic specific amylase, Hb A1c, ALT, AST, creatinine, triglyceride, total cholesterol, HDL, LDL, and stool samples were taken for the determination of Fecal Elastase 1.

The blood samples were centrifuged at 4000 rpm for 5 minutes and separated from their serum and plasma. The serum and stool samples obtained were stored at -20 oC until analysis. Before the study, all stool samples were carefully rotated and mixed, waiting for them to reach room temperature (15–18 C). All samples were examined on the same day to avoid possible differences.

Biochemical parameters were studied in the cI16200 model autoanalyzer with Abott brand commercial kits. HbA1c was studied in Adams TM A1C HA-8180T (ARKRAY) device with HPLC method. Human Fecal Elastase (Catalog no: YLA1650YU), human adiponectin

(Catalog no. YLA1823HU), Human Leptin (YLA1318HU) were studied in the Bio-Tex ELX800 model ELIDA reader with ELISA kits.

Body Mass Index (BMI) was calculated by dividing the weight of the participants by the square of their height. Insulin resistance was calculated using the HOMA-IR index ((Fasting blood glucose x Fasting blood insulin level) / 405 formula); Values of 2.5 and above were considered significant. After looking at fasting glucose to exclude the diagnosis of diabetes, 75gr OGTT was performed as needed.

Statistical Data Analysis

SPSS 22 (SPSS Inc. Chicago.IL.USA) program was used for statistical analysis of the data. Descriptive statistics; frequency tables and cross tables were used for categorical variables; numerical variables were given as mean, median, standard deviation, minimum and maximum. Chi-Square was used to compare independent categorical variables, T-Test was used in cases where normal distribution was provided in binary group comparisons, and Mann-Whitney U test was used in cases where normal distribution was not provided. Pearson correlation analysis was used to determine the relationship between numerical variables. Linear Regression analysis was used to determine risk factors. Statistical significance level is $p < 0.05$.

Results

The patient group consisted of 38 women 5 men and the control group 33 women 10 men. Statistically, both groups were similar for gender and age (p: 0.25, 0.11, respectively). (Table 1, 2)

BMI and HOMA-IR were significantly higher in the insulin resistance group (p: 0.00, 0.00, respectively) (Table 2). While the lowest and highest BMI in the IR group were 20.58-44, these values were 18.7-37.3 in the controls. While 31 of the patients had BMI≥30 (74%), this number was only 13 (28%) in the control group. In the control group, HOMA-IR level was <2 in 29 participants, but HOMA-IR level was <2.5 in all. In the IR group, all HOMA-IR levels were 2.5 and above.

Fecal Elastase-1 levels were significantly lower in the IR group (p: 0.00). There was no significant difference between the groups for blood, AST, ALT, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, pancreatic amylase, lipase levels (p: 0.94, 0.07, 0.93, 0.94, 0.17, 0.32, 0.48, 0.69, respectively) (Table 3, 4). Blood glucose, insulin and HbA1C levels were significantly higher in the patient group than in the control (p: 0.00, 0.00, 0.00, respectively) (Table 4). The lowest and highest HbA1c levels in the IR group were 4.7-5.9 (≥5.7; n: 8), while in the control group they were 4.3-5.6.

Leptin levels were significantly higher in the IR group than the controls (p: 0.01). Although there was no significant difference between the groups for adiponectin levels, the it was lower in the IR group (p: 0.17; 3.75 vs 4.87, respectively) (Table 4).

In the Pearson correlation analysis performed within the group with insulin resistance, a significant positive relationship was found between HOMA-IR and Adiponectin (p: 0.022 r: +0.34).

A significant positive relationship was found between HOMA-IR and Adiponectin in the Pearson correlation analysis performed within the group with insulin resistance (p: 0.022 r: 0.34). However, this significance was not found in the control group analysis (p: 0.88). There was a significant negative relationship between pancreatic amylase and HOMA-IR (p: 0.029, r: -0.33), a significant negative relationship between FE-1 and Adiponectin (p: 0.038, r: -0.31), a positive relationship between HbA1C and age (p: 0.014, r: 0.37), and a significant positive relationship between Leptin and Adiponectin (p: 0.00, r: 0.59). In addition, there was a negative relationship between insulin levels and FE-1, although it was not significant (p: 0.07, r: -0.027) (Table 5).

In multiple linear regression analysis with all cases (n: 85), only HOMA-IR was found to have a negative effect on FE-1 (p: 0.004, β: -0.404) (Table 6).

Discussion

As a result of the study, it was revealed that diabetes affects the exocrine function of the pancreas in parallel with glycemic dysregulation. Exocrine and endocrine pancreatic function has been shown to decrease secondary to hyperglycemia and hyperinsulinemia. [11] Ewald et al., found a positive correlation between FE-1 and C peptide in their study of diabetes groups except gestational diabetes.[12] In addition, pancreatic volume is known to decrease in type 2 diabetes. Philippe et al., also found that FE-1 level was lower in diabetic cases with low pancreatic volume, although it was not statistically significant.[13] This has been shown to be associated with FE-1[14] and HbA1C[15].

Tushuizen et al., found a negative relationship between pancreatic fat rate and beta cell function in men without diabetes, but this relationship was not detected in diabetics.[16] In this study, pancreatic fat ratio was negatively correlated with triglyceride, BMI, fasting blood glucose and glucose sensitivity of Beta cells regardless of age. There are studies showing that pancreatic fat accumulation is associated with BMI in non-diabetics rather than Diabetes Mellitus.[17] In relation to this, Teichmann et al., found pancreatic Fecal Elastase-1 level lower in non-diabetic obese women compared to the control group.[18] Likewise, we found that FE-1 levels were significantly lower in the insulin resistance group, 74% of which were obese, compared to the control group, of which only 28% were obese.

For the first time, Rathman et al., compared the cases as HbA1C 5.7-6.4 prediabet with HbA1C <5.7 non diabetic and found the FE1 level significantly lower in the group with higher HbA1C. They also found that the detection of FE1 <100mcg as an indicator of severe pancreatic exocrine insufficiency increased significantly in this group. This study suggests that pancreatic exocrine dysfunction may be a concomitant disorder rather than a complication of diabetes, as it is found at relatively lower HbA1C levels.[19]

Insulin resistance leading to metabolic syndrome causes fat deposition in visceral organs. It is thought that pancreatic fat accumulation may decrease pancreatic volume and cause an impaired endocrine function while simultaneously it may lead to an exocrine dysfunction before diabetes develops. This can be demonstrated by the HOMA-IR, HbA1C and FE-1 relationship. Unlike the study of Rathman et al., in our study, the highest HbA1C level was 5.9, and HbA1C was ≥5.7 in only 8 people in the insulin resistance group, and FE-1 levels were significantly lower in the insulin resistance group (HOMA-IR≥2.5). In addition, the rate of cases with FE-1 <100 mcg in the insulin resistance group was 13% (n: 6), which was not detected in the control. Again, in the IR group, a significant negative correlation was found between pancreatic amylase levels, another exocrine indicator of the pancreas, and HOMA-IR.

Adiponectin levels, an adipokine released from adipose tissue, are strongly associated with metabolic syndrome.[20] Even if BMI does not increase, the degree of visceral obesity and ectopic fat distribution occurring when adipose tissue storage capacity is exceeded is closely related to the decrease in the concentrations of adiponectin, an endogenous insulin sensitizer and anti-inflammatory adipokine. Thus, hypoadiponectinemia is associated with metabolic syndrome and insulin resistance.[21] In our study, although there was no significant difference between the Adiponectin levels of the two groups, we found a lower rate in the insulin resistance group. However, we found a significant inverse correlation between Adiponectin and FE-1. We interpreted this as a protective increase of Adiponectin against insulin resistance, while FE-1 decreased due to insulin resistance in early stage of insulin resistance. Because in this group, despite relatively decreased adiponectin levels, a positive correlation was observed between HOMA-IR and Adiponectin levels. No correlation was found in the group without insulin resistance. Perhaps the absence of a significant difference between Adiponectin levels may indicate early insulin resistance. This may suggest that FE-1 is very sensitive to insulin resistance.

Blood levels of Leptine, another adipokine released from adipose tissue, reflect the amount of total body energy as well as acute changes in energy intake; it regulates appetite and body fat mass, and in the hypo and normoleptinemic state, it mainly regulates the energy balance by suppressing appetite. [22] [23] Increased leptin levels are directly related to obesity, secondly to leptin resistance and cardiovascular health.[10] In accordance with the literature, we found that Leptin levels were significantly higher in the insulin resistance group, which was found to include obesity patients (74% to various degrees). We did not find any relationship between FE-1 and Leptin levels.

In the literature, we did not find any study investigating the relationship between insulin resistance, Adiponectin, Leptin and FE-1. Our study is the first study on this subject. The low number of cases and the inclusion of patients to study only by questioning acute or chronic pancreatitis stories of gastrointestinal disease without any imaging are the weaknesses of our study. There is a need for studies with larger case series on this subject.

In conclusion, our study is the first study to investigate the relationship between FE-1 and insulin resistance. Our finding shows that pancreatic exocrine function is sensitive to the bad effects of insulin resistance and also indicates that exocrine pancreatic disruption is simultaneous with the endocrine pancreas in the diabetes development process.

REFERENCES

[1] Forsmark CE. Diagnosis and management of exocrine pancreatic insufficiency. Curr Treat Options.Gastroenterol.2018 & 16(3):306–315.
[2] Lüth S, Teyssen S, Forssmann K, Kölbel C, Krummenauer F, Singer MV. Fecal elastase-1 determination: 'gold standard' of indirect pancreatic function tests? Scand J Gastroenterol. 2001 Oct; 36(10):1092-9.PMID:11589385
[3] Chr Löser, A Möllgaard, U R Fölsch. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function tes. Gut 1996; 580-586, 39:
[4] Saisho Y, Butler AE, Meier JJ, et al. Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes. Clin Anat. 2007;20(8):933–942.
[5] Keller J., Layer, P.Human pancreatic exocrine response to nutrients in health and disease.Gut. Volume 54, Issue SUPPL. 6, 2005, Pages vi1-vi28
[6] Kahn SE, Hull RL, Utzschneider KM: Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 14: 840–846, 2006
[7] Physiology, Endocrine, Pancreas Suzan A. ElSayed1; Steve S. Bhimji. Last Update: October 17, 2017.
[8] Ziemke F, Mantzoros CS. Adiponectin in insulin resistance: lessons from translational research. Am J Clin Nutr. 2010 Jan;91(1):258S-261S. doi: 10.3945/ajcn.2009.28449C. Epub 2009 Nov 11. Review. PubMed PMID: 19906806; PubMed Central PMCID: PMC2793112.

[9] Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia. 2003 Apr;46(4):459-69. Epub 2003 Apr 10. PubMed PMID: 12687327.
[10] Li LJ, Rifas-Shiman SL, Aris IM, Mantzoros C, Hivert MF, Oken E. Leptin trajectories from birth to mid-childhood and cardio-metabolic health in early adolescence. Metabolism. 2019 Feb;91:30-38. doi: 10.1016/j.metabol.2018.11.003. Epub 2018 Nov 7. PubMed PMID: 30412696; PubMed Central PMCID: PMC6366620.
[11] Lam WF, Gielkens HA, Coenraad M , Souverijn JH , Lamers CB , Masclee AA . Effect of insulin and glucose on basal and cholecystokinin-stimulated exocrine pancreatic secretion in humans. Pancreas [01 Apr 1999, 18(3):252-258]

[12] Ewald, N.Email Author, Raspe, A., Kaufmann, C., Bretzel, R.G., Kloer, H.U., Hardt, P.D. Determinants of exocrine pancreatic function as measured by fecal elastase-1 concentrations (FEC) in patients with diabetes mellitus. European Journal of Medical
[13] Philippe M.-F., Benabadji, S., Barbot-Trystram, L.Vadrot, D., Boitard, C., Larger, E. Pancreatic volume and endocrine and exocrine functions in patients with diabetes. Pancreas. Volume 40, Issue 3, April 2011, Pages 359-363.
[14] Bilgin, Mehmet, Balci, Numan Cem; Momtahen, Amir Javad, Bilgin, Yaşar; Klör, Hans-Ulrich; Rau, Wigbert S. MRI and MRCP Findings of the Pancreas in Patients With Diabetes Mellitus: Compared Analysis With Pancreatic Exocrine Function Determined by Fecal Elastase. Journal of Clinical Gastroenterology: February 2009 - Volume 43 - Issue 2 - p 165-170 doi: 10.1097/MCG.0b013e3181587912
[15] Soo Lim, Jae Hyun Bae, Eun Ju Chun, Haeryoung Kim, So Yeon Kim, Kyoung Min Kim, Sung Hee Choi, Kyong Soo Park, Jose C. Florez,Hak Chul Jang. Differences in pancreatic volume, fat content, and fat density measured by multidetector-row computed tomography. Acta Diabetol. 2014 Oct;51(5):739-48. doi: 10.1007/s00592-014-0581-3. Epub 2014 Mar 27.

[16] Maarten E. Tushuızen, Mathıjs C. Bunck, Petra j. Pouwels, Saskıa Bontemps, Jan Heın T. Van Waesberghe, Roger K. Schındhelm, Andrea Marı, Robert J. Heıne, Mıchaela Dıamant. Pancreatic Fat Content and -Cell Function in Men With and Without Type 2 Diab. Diabetes Care 2007 Nov;30(11):2916-21. doi: 10.2337/dc07-0326. Epub 2007 Jul 31.
[17] Y. Saisho, A.E. Butler, J.J. Meier, T. Monchamp , M. Allen−Auerbach, R.A. Rizza, P.C. Butler. Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type−2 diabetes. Clinical anatomy 20:933-942 (2007)

[18] J.Teichmann, J.F.Riemann,U.Lange.PrevalenceofExocrinePancreaticInsufficiencyinWomenwith ObesitySyndrome:AssessmentbyPancreaticFecalElastase1.ISRN Gastroenterology Volume 2011, Article ID 951686, 5 pages doi:10.5402/2011/951686
[19] Rathmann W, Haastert B, Oscarsson J, Berglind N, Wareham NJ. Inverse association of HbA1c with faecal elastase 1 in people without diabetes. Pancreatology. 2015 Nov-Dec; 26601880, 15(6):620-5.
[20] Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol. 2004 Jan;24(1):29-33. Epub 2003 Oct 9. Review. PubMed PMID: 14551151.

[21] Boutari C, Mantzoros CS. Inflammation: A key player linking obesity with malignancies. Metabolism. 2018 Apr;81:A3-A6. doi: 10.1016/j.metabol.2017.12.015. Epub 2018 Jan 6. PubMed PMID: 29309747.
[22] Bidulescu A, Liu J, Hickson DA, Hairston KG, Fox ER, Arnett DK, Sumner AE,Taylor HA, Gibbons GH. Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in African Americans: the Jackson Heart Study. BMC Cardiovasc Disord. 2013 Feb 22;13:9. doi: 10.1186/1471-2261-13-9.
PubMed PMID: 23433085; PubMed Central PMCID: PMC3586352.
[23] Elbers JM, Asscheman H, Seidell JC, Frölich M, Meinders AE, Gooren LJ. Reversal of the sex difference in serum leptin levels upon cross-sex hormone administration in transsexuals. J Clin Endocrinol Metab. 1997 Oct;82(10):3267-70. PubMed PMID: 9329351.