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Selective Association of Electrocardiographic Abnormalities with Insulin Sensitivity and Beta-Cell Function in Type 2 Diabetes Mellitus: a Cross Sectional Analysis

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Abstract

Background—We investigated the association of electrocardiographic (ECG) abnormalities with markers of insulin resistance and pancreatic beta-cell dysfunction in a cross-sectional study of type 2 diabetic patients.

Methods—ECG criteria were evaluated in the Penn Diabetes Heart Study (PDHS) participants (n=1671; 64% male; 61% Caucasian), including a sub-sample (n=710) that underwent oral glucose tolerance testing (OGTT). The Matsuda Insulin Sensitivity Index (MISI) and homeostasis model assessment of insulin resistance (HOMA-IR) estimated insulin sensitivity; Insulinogenic Index (IGI) and homeostasis model assessment of beta-cell function (HOMA-B) assessed beta-cell function. Multivariable regression modeling was used to analyze associations of ECG changes with these indices.

Results—In unadjusted analyses, subjects in the highest quartile of MISI had the lowest prevalence of Q-waves (6.3% vs. 15.3%, p = 0.005). In adjusted models, an inverse association was seen between Q-waves and log MISI [one standard-deviation (SD) increase; OR=0.59 (95% CI 0.43–0.87 p = 0.001)]. In the full PDHS, there was a direct association between Q-waves and HOMA-IR [one SD increase; OR=1.43 (95% CI 1.13–1.81, p = 0.003)]. In adjusted models, left ventricular hypertrophy (LVH) also was inversely associated with MISI and directly with HOMA-

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AUTHORS CONTRIBUTIONS

A.B.B. contributed to data collection, conducted statistical analyses, interpreted findings, and had primary responsibility for writing the manuscript. C.K.M, A.N.Q, J.V.N, S.B.P, contributed to data collection and management. M.R.R. and N.I. provided endocrinology expertise for the analysis and interpretation of results and reviewed/edited the manuscript. M.P.R. and N.I. were responsible for project conception, statistical analysis, interpretation of results, and manuscript writing with A.B.B. All authors have approved the manuscript for submission. M.P.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

IR. Higher IGI scores were associated with a lower prevalence of nonspecific ST changes [OR=0.78 (95% CI 0.62–0.98, p = 0.032)].

Conclusions—In type 2 diabetic patients, both OGTT- and HOMA-derived measures of insulin resistance were associated with pathologic Q waves and LVH on ECGs.

Keywords

ECG; insulin sensitivity; beta-cell function; MISI

INTRODUCTION

Insulin resistance and diminished insulin secretion by pancreatic beta-cells are fundamental pathophysiologic mechanisms in the development of type 2 diabetes mellitus (1). While there remains debate regarding the relative contribution of either abnormality in individuals, it is clear that by the time clinical hyperglycemia develops, both are significantly abnormal (2). There are few studies that have explored the association between cardiovascular traits and measures of both insulin resistance and pancreatic beta-cell dysfunction within the same study sample.

Type 2 diabetes is a strong predictor of cardiovascular disease (CVD) (3) and multiple studies have shown an association between insulin resistance and CVD in both diabetic (4–5) and non-diabetic (6) patients. However, the relation of pancreatic beta-cell dysfunction to CVD is less studied. Unlike microvascular complications of diabetes, cardiovascular events may not relate strongly to glycemic control or respond to the treatment of hyperglycemia (7). In contrast, the degree of insulin resistance within type 2 diabetes has strong associations with the risk of macrovascular complications independent of traditional risk factors (8).

Multiple measures have been developed to quantify insulin resistance and glucose homeostasis in vivo in an effort to investigate the physiology and epidemiology of type 2 diabetes. OGTT-derived MISI reflects both hepatic and peripheral skeletal muscle insulin sensitivity. Conversely, the OGTT-derived IGI is a measure of first-phase insulin secretion and beta-cell function. OGTT-derived indices are easier to perform than direct measures of insulin sensitivity, and the MISI is highly correlated with the gold standard hyperinsulinemic-euglycemic clamp test (9–10). It is not clear if OGTT-derived measures are superior to static, fasting parameters, such as HOMA-IR and HOMA-B. While HOMA indices have been associated with CVD traits in prior studies (11–12), it is unclear if MISI or IGI provide incremental value regarding the risk of cardiovascular complications of diabetes.

Major and minor ECG abnormalities are established prognostic indicators of CVD (13). Impaired glucose tolerance and type 2 diabetes associate with electrocardiographic evidence of CVD (14–15). No studies to date, however, have compared the relationship between OGTT measures of insulin resistance and beta-cell function with ECG abnormalities. In this analysis of PDHS, a cross-sectional study of patients with type 2 diabetes without known CVD (16–17), we examined the relationship of OGTT-derived MISI and IGI data with ECG

abnormalities. We then compared these relationships to the fasting glucose and insulin derived HOMA-IR and HOMA-B.

MATERIALS AND METHODS

Study participants and protocol

Details regarding PDHS have been previously reported (16–17). Briefly, PDHS is a cross-sectional, single-center study of risk factors for heart disease in type 2 diabetic patients (n=2120) without clinical evidence of CVD (defined as myocardial infarction, documented angiographic coronary artery disease, positive stress test, percutaneous coronary or peripheral intervention, coronary artery or peripheral artery bypass grafting, stroke, or transient ischemic attack). Subjects were recruited between 2000 and 2011, obtaining baseline ECGs upon enrollment. Included in PDHS were: patients aged 35–75 with a clinical diagnosis of type 2 diabetes in the patient medical record (defined as fasting blood glucose ≥126 mg/dl, 2-h postprandial glucose ≥200 mg/dl, or use of oral hypoglycemic agents or insulin in a subject > 40 years of age). Exclusion criteria were a serum creatinine > 2.5 mg/dl, clinical diagnosis of type 1 diabetes or weight > 300 lbs. The University of Pennsylvania Institutional Review Board approved the study and informed consent was obtained from all study participants.

Study participants were evaluated at the General Clinical Research Center after a 12-hour overnight fast. Complete blood count, routine chemistries, glucose, lipids, and hemoglobin A1c (HbA1c) were drawn. A questionnaire regarding medical, family, and social history, medication use, and cardiac history was completed. Hypertension was defined as taking antihypertensive medications or blood pressure higher than 130/80 mmHg. We chose >130/80mmHg as our definition of hypertension because this is the goal BP for diabetic patients according to JNC-7 guidelines, the major guideline used to define hypertension during the recruitment of our study. Framingham risk scores were calculated as described (17).

Study parameters

Enrollment ECGs were available in 2085 of 2120 PDHS participants. Abnormalities were graded according to the Minnesota Code, which has been well validated (18), and detailed ECG criteria can be found in the Minnesota Code Manual of Electrocardiographic Findings (38). Briefly, for our analyses, intervals, rhythm, axis, and presence of block were recorded. The following three criteria had to be present in at least two localizing leads to be considered a pathologic Q-wave MI in our study: a Q-wave deflection of at least 1mm in amplitude, a Q/R amplitude ratio ≥ 1/3 and Q-wave duration ≥ 0.03 seconds. Criteria for LVH were according to code 3.1 and 3.3 in the Minnesota Code. The presence of nonspecific ST-T wave changes and the presence of Q–wave myocardial infarction (MI) were recorded using a modified version of the Minnesota Code. As patients were asymptomatic during the time of their presentation for this study, the presence of T wave abnormalities, or a flattened or depressed ST segment in at least two consecutive localizing leads were considered to be nonspecific, and recorded as so.

Between 2007 and 2011, a subgroup of PDHS participants underwent a 2-hour OGTT (75g glucose load with blood sampling at baseline and 30, 60, and 120 minutes). Of 990 eligible subjects, 883 completed OGTT, while 107 subjects did not (Supplemental Figure 1). Subjects who underwent OGTT but had a baseline fasting glucose >200mg/dL (n=81) or baseline insulin >125μIU/mL (n=7) were excluded from analysis because of possibility of incomplete overnight fast, exogenous insulin use the morning of OGTT, or glucotoxicity (i.e., glucose impairment of beta-cell function). After additional exclusion of subjects with a history of gastric bypass surgery (19) (n=6) or missing covariate data (n=79), the final OGTT sample for analysis was 710. Whole-body insulin sensitivity was estimated by calculating MISI as described (9–10): $10{,}000/(G_0 \times I_0 \times G_m \times I_m)^{0.5}$, where G_0 and I_0 are pre-glucose load values for glucose and insulin (in mg/dL and μIU/mL, respectively) and G_m and I_m are mean post-glucose load values. IGI was calculated (9) as the ratio of the change of plasma insulin (μIU/mL) to the change in glucose concentration (mg/dL) between time zero and thirty minutes of OGTT: $\Delta I\ (0–30)/\Delta G\ (0–30)$.

Data for HOMA parameters were available in PDHS including in all those who participated in OGTT. Applying the same exclusion criteria as described above for the OGTT subsample, HOMA metrics were calculated in the PDHS sample (n=1671). We calculated HOMA-IR as a measure predominantly of hepatic insulin resistance in the fasting state (9, 20): (glucose [mg/dL] x insulin [μIU/mL])/405. HOMA-B {360 x insulin [μIU/mL]/(glucose [mg/dL] – 63)} was calculated in the subset of participants not on insulin therapy (HOMA-B has not been validated in those taking insulin exogenously) as an alternative fasting-state measure of beta-cell function (9, 20). We selected these HOMA indices for comparative analysis based on their use in previous investigations and large-scale population-based studies (9, 20).

Statistical Analysis

Data are reported as median ± interquartile range (IQR) for continuous variables and as percentages for categorical variables. The IGI, MISI, HOMA-IR, and HOMA-B were not normally distributed; thus, MISI (natural log-transformed, i.e. “Ln-MISI”), IGI (inverse normal transformation to accommodate negative values, i.e. “Inv-IGI”), HOMA-IR (natural log-transformed, i.e. “Ln-HOMA-IR”), HOMA-B (natural log-transformed, i.e. “Ln-HOMA-B”), were transformed to facilitate modeling as continuous variables.

We performed logistic regression and report multivariable-adjusted associations for an increase in one standard deviation for Ln-MISI, Inv-IGI, Ln-HOMA-IR and Ln-HOMA-B with the presence of different baseline ECG abnormalities as defined above. We tested for associations with ECG changes in incremental models adjusting for potential confounders: Model 1: age, gender, race; Model 2: Model 1 plus history of hypertension, duration of diabetes, Framingham risk score (FRS), body-mass index (BMI), mean systolic blood pressure (mean SBP), mean diastolic blood pressure (mean DBP), direct low-density lipoprotein (LDL-C); Model 3: Model 2 plus medications (beta-blockers, calcium channel blockers, ACE-inhibitors, aspirin, insulin, metformin, sulfonylureas, sitagliptin, and lipid lowering agents). These analyses were carried out for HOMA data in the full PDHS sample as well as for OGTT and HOMA data in the OGTT sub-group. Odds ratio testing examined interactions of specific variables with age, race and gender; as these results were not

significant, no stratified analyses are presented. All analyses were done using STATA version 12.0 software (Statacorp, College Station, Texas).

RESULTS

Characteristics of the study population

The characteristics of the PDHS sample with complete HOMA and ECG data (n=1671) and the OGTT subgroup (n=710) were similar (Table 1). For the full HOMA sample, the mean age was 60 (IQR 54–66), 64% were male, 62% were Caucasian and 33% were African American. For the OGTT subgroup, the mean age was 60 (IQR 54–65), 65% were male, 60% were Caucasian, and 34% were African American. Average HbA1c values (6.6 to 6.5%) as well as duration of diabetes, BMI, incidence of baseline ECG changes and diabetic indices also were similar in the OGTT subgroup and full HOMA sample (Table 1).

Prevalence of ECG changes by OGTT and HOMA criteria

Table 2 shows the association of ECG changes across quartiles of MISI and IGI in the OGTT subgroup and for HOMA indices in the OGTT subgroup as well as full PDHS sample. In unadjusted analysis of the OGTT subgroup, those with the highest insulin sensitivity, as reflected by the highest quartile of MISI or the lowest quartile of HOMA-IR, had lower prevalence of Q-waves (p=0.005 and p=0.018, respectively) (Table 2). This was also true for the lowest HOMA-IR quartile in the full sample (p=0.007) (Table 2). Left ventricular hypertrophy (LVH) prevalence increased with greater insulin resistance but this reached statistical significance only for association with HOMA-IR in the full sample (p<0.001). Finally, nonspecific ST changes had a lower prevalence in those with highest IGI (p =0.04). There was no association of any other ECG measures (heart rate, PR, QRS and QTc intervals) with OGTT and HOMA parameters in crude or adjusted models (not shown).

Insulin resistance is associated with Q-waves

In multivariable models of the OGTT sub-sample, there was an inverse association between MISI data and the odds for Q-waves in all three models (Table 3); e.g., in fully adjusted models OR=0.59 (95% CI 0.43–0.87, p = 0.001) for one standard deviation (SD) increase in the Ln-MISI. This association was further supported by analysis of HOMA-IR data in the OGTT sub-cohort and the full sample (Table 3), where there was a direct association between one SD increase in the Ln-HOMA-IR and the odds of Q waves. In sensitivity analyses, findings were consistent when quartiles of MISI and HOMA-IR rather than continuous variables were modeled (not shown). Thus, analyses of both OGTT data and fasting HOMA parameters suggest that reduced insulin sensitivity in type 2 diabetes is associated with pathologic Q-waves, an electrocardiographic marker of cardiac injury typically caused by myocardial infarction.

Insulin resistance also associates with LVH

In multivariable modeling, MISI data were inversely associated with LVH in the OGTT subgroup; e.g., in fully adjusted models OR=0.50 (95% CI 0.25–0.98, p = 0.043) for one SD increase in the Ln-MISI (Table 3). Similarly, there was direct association between one SD increase in the Ln-HOMA-IR and the odds of LVH in the OGTT subsample; statistical

significance was stronger for LVH and Ln-HOMA-IR in the full sample (Table 3). In sensitivity analyses, findings were consistent when quartiles of MISI and HOMA-IR were used (not shown). These data suggest that LVH, an electrocardiographic marker of ventricular remodeling and cardiomyopathy, is more prevalent in type 2 diabetic patients with greater insulin resistance, whether assessed by fasting HOMA parameters or OGTT-derived measures.

The insulinogenic index of pancreatic beta-cell function is inversely associated with nonspecific ST-T wave changes

The IGI and HOMA-B were not associated with Q waves or LVH in crude or fully adjusted models (Supplementary Table 1). In contrast, there was a significant inverse association between IGI data and the odds of ST changes (Table 3), most pronounced in the fully adjusted model, OR=0.78 (95% CI 0.62–0.98, p = 0.032) for one SD increase in the Inv-IGI. Although trends were similar, the association of HOMA-B with ST-T wave changes did not reach statistical significance in the OGTT sub-sample or in the full PDHS sample (Table 3). The presence of ST-T wave changes on ECG did not relate to the MISI or HOMA-IR in any multivariable models (Supplementary Table 1). Though nonspecific ST changes often do not correlate with specific clinical disorders, this finding may suggest that as pancreatic beta-cell function declines in type 2 diabetes, cardiac function is negatively impacted.

CONCLUSIONS

Rates of both ischemic and non-ischemic heart disease are increased in diabetic patients (3, 6, 8). Traditional cardiovascular risk factors, however, fail to account fully for the increased cardiovascular events in diabetes (6). We examined the relationship of fasting and OGTT-evoked measures of insulin sensitivity and pancreatic beta-cell function with specific ECG changes. We analyzed these associations in a large sample of type 2 diabetic patients without clinical evidence of heart or kidney disease at recruitment. Electrocardiographic evidence of myocardial infarction (Q-waves) and cardiac remodeling (LVH) had consistent patterns of associations with both the MISI (surrogate of both peripheral and hepatic insulin sensitivity) and the fasting HOMA-IR (measure of hepatic insulin resistance). In contrast, neither measure of pancreatic beta-cell function was associated with major ECG changes (e.g., Q-waves and LVH).

We found that patients with increased insulin resistance had higher odds of having pathologic Q-waves than those with more preserved insulin sensitivity. The presence of Q-waves is a marker of myocardial infarction, coronary atherosclerosis and increased cardiovascular risk (21). Insulin has a significant role in atherogenesis, and is known to stimulate endothelial nitric oxide production and increase blood flow to skeletal muscle, facilitating uptake of glucose. The development of endothelial insulin resistance may result in imbalance between nitric oxide production and endothelin secretion, leading to endothelial dysfunction (22). Surrogate measures of endothelial dysfunction are independently associated with atherosclerosis, myocardial infarction and death (23). Thus, endothelial insulin resistance and dysfunction is one mechanism that may explain the association of Q-wave association with measures of insulin resistance. However, not all

studies are consistent in the relationship of insulin resistance with endothelial dysfunction (22, 24–25).

The presence of LVH on ECG carries significant cardiovascular risk (26–27), and is a specific, but less sensitive, marker of cardiac dysfunction (28). Patients with LVH on ECG have higher left ventricular mass index, lower ejection fraction percentages and increased prevalence of diastolic dysfunction via echocardiography than those without (29–30). Patients with LVH may have increased cardiovascular risk independent of echocardiographic evidence of cardiomyopathy (28). Our findings suggest that increasing insulin resistance is associated with LVH on ECG in diabetic patients. This likely reflects both hypertensive as well as diabetic cardiomyopathic processes. Multiple studies have identified an association between diabetes and sub-clinical cardiomyopathy independent of hypertension via echocardiography and cardiac MRI (31–33). Diabetic cardiomyopathy is considered a distinct entity consisting of concentric LVH, dilated cardiomyopathy, diastolic dysfunction and fibrosis in the absence of coronary artery disease and hypertension (31). Lipotoxicity-induced myocyte apoptosis related to cardiac insulin resistance is one proposed mechanism of diabetic cardiomyopathy that may contribute to our observed association. Mitochondrial dysfunction with diminished ATP production has also been noted in diabetic hearts (31). The presence of LVH in our study does not differentiate between diabetic, hypertensive and ischemic cardiomyopathic processes; thus, further studies are warranted.

Although nonspecific ST-T wave changes on resting ECGs can be attributed to youth, hyperventilation, food ingestion and electrolyte disturbances, several studies have shown them to be markers of increased cardiovascular risk and coronary disease (21, 34); however, there is substantially less risk when compared to major ECG changes, such as pathologic Q-waves and LVH (21). Prior studies have included mostly non-diabetic subjects. Our study of asymptomatic type 2 diabetic patients without known clinical heart disease showed a high prevalence (~20%) of nonspecific ST-T wave changes. This may be attributable to a higher prevalence of subclinical cardiomyopathy or silent CAD in Type 2 diabetes. Albeit quite modest, the observed association of ST-T wave changes with the OGTT IGI warrants further study to determine if measures of pancreatic beta-cell function have subtle relation to cardiac dysfunction in type 2 diabetes. Our findings are clear, however, in demonstrating that measures of insulin resistance, but not of beta-cell dysfunction, have robust associations with major ECG changes such as pathologic Q-waves and LVH.

We employed two complementary approaches to examine the relation with ECG abnormalities: OGTT-derived and fasting HOMA indices. Fasting HOMA indices provide a window into hepatic insulin sensitivity (suppression of hepatic glucose production; HOMA-IR) and basal beta-cell function (HOMA-B) (9). The OGTT-derived measures may more accurately reflect the dynamic physiology and give insights into peripheral disposal of glucose (MISI) and beta-cell function (IGI) in response to acute glucose stimulation (9–10). Given our large sample size it was impractical to compare these measures to the gold standard clamp technology in assessing insulin sensitivity or beta cell function (9–10, 20, 35). We did, however, use log transformation of these indices because such normalization has been shown to correlate better with clamp studies in those with impaired glucose tolerance, and likely type 2 diabetes (36).

Multiple studies have shown a higher correlation between clamp measures of insulin sensitivity and MISI than HOMA-IR in non-diabetic samples (36–37). In this context, we interpret our finding of consistent associations of *both* the MISI and HOMA-IR with pathologic Q-waves and LVH as evidence of a robust relation between insulin resistance and these major ECG abnormalities. In contrast, the association of ST-T wave changes to beta-cell dysfunction was only observed for the IGI and not the HOMA-B measure. This suggests one of two possibilities: (1) IGI may be a more accurate measure of changes in pancreatic beta-cell dysfunction than HOMA-B, or (2) the association between ST-T wave changes and IGI might have arisen by chance. Additional studies would be necessary to differentiate between these two possibilities.

Our study has several strengths and some weaknesses. This is the largest investigation to date of OGTT-derived indices of insulin resistance and beta-cell function in diabetic individuals with ECG abnormalities. Complementary OGTT and fasting parameters of insulin sensitivity and beta-cell function were employed. Patients with clinical CVD were excluded, permitting an examination of associations of insulin homeostasis and ECG changes prior to development of overt clinical disease.

A limitation of this study is that it was cross-sectional. Although we cannot prove causality based on our associations, we provide potential physiologic explanations. Also, given our relatively large sample, it was impractical to validate findings with gold standard clamp studies. Consistent with recruitment excluding clinical CVD, the PDHS sample has a low prevalence of LVH and pathologic Q-waves, which can limit the power of the analyzed associations. Also, there is substantial intra-individual variation in minor ST-T wave changes over time (21); thus, we may have over- or underestimated the presence and impact of ST-T wave changes.

Though there is a paucity of data on the correlation of ECG and MRI abnormalities in diabetes, many studies have shown the correlation between ECG changes and echocardiographic changes (28–31). A significant limitation of our study is that we did not have imaging studies to further characterize the nature of cardiomyopathy—if any—associated with specific ECG changes and metabolic profiles. Therefore, how the associations we describe relate to cardiac pathology is unclear. Structural and molecular imaging will be important components of future studies to help elucidate the association of insulin resistance, ECGs and specific structural and functional pathologies.

Finally, our study sample was recruited between 2000 and 2011. This was prior to the use of HbA1c criteria for diagnosis of diabetes. Thus, we did not use HbA1c as part of our diagnostic or inclusion criteria for this study.

In conclusion, in asymptomatic type 2 diabetic patients without clinical CVD, both OGTT- and HOMA-derived measures of insulin resistance were associated with pathologic Q waves and LVH on ECGs. This suggests a potential role for systemic, endothelial or cardiac insulin resistance in the cardiac remodeling seen in ischemic and non-ischemic cardiomyopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of the PDHS Sample and the OGTT Subsample

Variable	OGTT Subsample n = 710 [IQR]	Full HOMA Sample n = 1671 [IQR]
Age (years)	60 [54–65]	60 [54–66]
Male (%)	65.4	64.4
Race (%)		
Caucasian	59.7	61.8
African American	34.4	32.6
Other	5.9	5.6
Hypertension (%)	67.2	64.7
Systolic BP (mmHg)	130 [21–141]	130 [121–141]
Diastolic BP (mmHg)	75 [71–82]	76 [71–82]
Hyperlipidemia (%)	71.8	70.2
LDL-C (mg/dL)	88 [103–89]	94 [77–116]
Tobacco, ever (%)	55.9	58.7
Diabetes duration (years)	6 [3–12]	6 [2–10]
BMI (kg/m2)	32.5 [28–37]	32.0 [28–36]
ECG changes		
Heart Rate (beats/min)	68 [61–77]	68 [62–77]
PR interval (msec)	163 [148–180]	162 [148–180]
QRS interval (msec)	90 [84–96]	90 [84–96]
QTc interval (msec)	412 [401–425]	414 [402–427]
BBB (%)	5.9	6.6
LVH (%)	2.4	2.3
Q waves (%)	9.4	7.1
ST changes (%)	18.0	18.2
Medications (%)		
ACE-Inhibitor	63.9	61.2
Beta-blocker	15.9	14.9
Calcium Channel Blocker	18.0	18.4
Aspirin	43.8	44.0
Lipid lowering agent[a]	64.4	61.1
Statin	59.9	56.3
Insulin	22.0	19.3
Metformin	68.3	64.6
Sulfonylurea	31.6	34.9
Sitagliptin	10.1	4.8
Diabetic indices		
HOMA-IR	4.4 [2.9–7.1]	4.3 [2.8–6.7]
HOMA-B%	106.3 [66.5–175.6]	105.2 [63.5–177.4]
Matsuda ISI	2.5 [1.7–3.7]	-

Variable	OGTT Subsample n = 710 [IQR]	Full HOMA Sample n = 1671 [IQR]
IGI (μU/mL per mg/dL)	0.2 [0.1–0.5]	-
Fasting insulin (μIU/mL)	15.3 [10.6–23.6]	14.8 [10.4–21.3]
Fasting glucose (mg/dL)	117 [100–138]	112 [93–134]
2-hr Plasma Glucose (mg/dL)	241 [189–296]	-
HbA1c (mmol/mol)	49 [42–56]	50 [43–61]
HbA1c (%)	6.5 [6–7.3]	6.6 [6.1–7.3]

Characteristics of the study sample are presented. Data are presented as median [IQR] or as percentages, except as indicated. MISI and IGI could not be calculated for subjects who did not undergo OGTT testing. 2-hour plasma glucose values were only available for the OGTT subsample.

[a] Includes statin use

Abbreviations: BMI=body mass index, BBB=bundle branch block, LVH=left ventricular hypertrophy, BBB=bundle branch block, OGTT=oral glucose tolerance testing, HOMA-IR=homeostatic model assessment of insulin resistance, HOMA-B=homeostatic model assessment of beta-cell function, Matsuda ISI=Matsuda insulin sensitivity index, IGI=Insulinogenic Index, HbA1c=hemoglobin A1c

Table 2

Prevalence of Baseline Electrocardiographic Abnormalities by Quartile of OGTT or HOMA Parameters

	Quartile 1 [range]	Quartile 2 [range]	Quartile 3 [range]	Quartile 4 [range]	p value [a]
OGTT-derived MISI[b]	[0.35–1.66]	[1.68–2.48]	[2.49–3.73]	[3.76–14.69]	
LVH (%)	4.0	1.7	2.3	1.1	0.12
Q (%)	15.3	8.6	8.0	6.3	0.005
ST-T (%)	16.5	18.3	18.2	20.0	0.42
OGTT-derived IGI[b]	[0.003–0.10]	[0.11–0.24]	[0.25–0.48]	[0.49–7.58]	
LVH (%)	2.8	1.2	4.0	1.1	0.66
Q (%)	11.3	7.5	7.4	12.0	0.84
ST-T (%)	22.0	21.3	13.1	16.0	0.04
HOMA-IR	[0.58–2.92]	[2.93–4.36]	[4.39–7.09]	[7.11–47.72] [e]	
	[0.51–2.84]	[2.85–4.27]	[4.28–6.73]	[6.75–47.72] [f]	
LVH (%)					
OGTT Subsample[b]	0.6	3.4	1.1	4.5	0.06
Total Sample[c]	1.0	2.3	2.3	5.4	<0.001
Q (%)					
OGTT Subsample[b]	6.7	7.3	10.1	13.6	0.018
Total Sample[c]	6.4	4.8	7.6	10.1	0.007
ST-T (%)					
OGTT Subsample[b]	15.7	20.3	18.5	17.5	0.78
Total Sample[c]	17.4	17.3	19.5	21.2	0.08
HOMA-B[d]	[14.53–66.46]	[66.58–106.24]	[106.40–175.59]	[175.84–6480.00] [e]	
	[14.53–61.41]	[61.57–100.15]	[100.22–167.53]	[168.00–3204.00] [f]	
LVH (%)					
OGTT Subsample	2.3	1.1	4.5	1.7	0.74
Total Sample	3.3	1.7	3.1	2.9	0.96
Q (%)					
OGTT Subsample	7.9	9.6	9.0	11.3	0.32

	Quartile 1 [range]	Quartile 2 [range]	Quartile 3 [range]	Quartile 4 [range]	p value [a]
Total Sample	6.8	6.8	7.2	8.0	0.45
ST-T (%)					
OGTT Subsample	21.9	19.8	14.6	15.8	0.07
Total Sample	19.8	18.1	19.7	17.8	0.59

[a] Statistical significance was tested using nonparametric test for trend across ordered groups, an extension of the Wilcoxon rank-sum test.

[b] OGTT Subsample n=710;

[c] Total Sample n=1671

[d] Participants on insulin therapy were excluded for analyses of HOMA-B leaving n=1334 for Total sample and n=554 for OGTT subsample

[e] Quartile ranges for participants in OGTT subsample

[f] Quartile ranges for participants in the total sample

Abbreviations: HOMA-IR=homeostatic model assessment of insulin resistance, HOMA-B=homeostatic model assessment of beta-cell function

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Table 3

Association of Insulin Sensitivity Metrics (A, B, C), and of Metrics of Pancreatic Beta-cell Function (D, E, F) with Electrocardiographic changes

	Pathologic Q waves		LVH		ST Changes	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
A. Ln-MISI[a] (per one SD increment)					**D. Inv-IGI** [a]	
Model 1	0.64	0.49–0.84	0.64	0.37–1.08	0.81	0.67–0.99
Model 2	0.65	0.48–0.87	0.65	0.36–1.17	0.81	0.66–1.00
Model 3	0.59	0.43–0.80	0.50	0.25–0.98	0.78	0.62–0.98
B. Ln-HOMA-IR [a] (per one SD increment)					**E. Ln-HOMA-B** [a]	
Model 1	1.51	1.16–1.98	1.64	1.00–2.68	0.76	0.57–1.01
Model 2	1.56	1.16–2.10	1.72	0.98–3.01	0.79	0.58–1.08
Model 3	1.75	1.26–2.43	2.28	1.17–4.43	0.82	0.60–1.13
C. Ln-HOMA-IR[b] (per one SD increment)					**F. Ln-HOMA-B** [c]	
Model 1	1.42	1.16–1.74	1.77	1.26–2.50	0.90	0.76–1.07
Model 2	1.36	1.09–1.70	1.86	1.27–2.69	0.88	0.74–1.06
Model 3	1.43	1.13–1.81	1.96	1.30–2.89	0.90	0.75–1.08

[a]OGTT Subsample (n=710);

[b]Total Sample (n=1671); Participants on insulin therapy were excluded for analyses of HOMA-B leaving n=1334 for full sample and n=554 for OGTT sub-sample

Adjusted for:

Model 1: age, gender, race

Model 2: Model 1 plus history of hypertension, duration of diabetes, FRS, BMI, mean SBP, mean DBP, LDL-C

Model 3: Model 2 plus medications (beta-blockers, calcium channel blockers, ACE-inhibitors, aspirin, insulin, metformin, sulfonylureas, sitagliptin, and lipid lowering agents)

Abbreviations: OR=Odds Ratio, CI=Confidence Interval, SD=standard deviations, Q=pathologic Q waves, LVH=left ventricular hypertrophy, Ln-MISI=natural log transformed matsuda sensitivity index, Ln-HOMA-IR=natural log transformed homeostatic model assessment of insulin resistance