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Ethnic Diversity in Beta-Cell Function Susceptibility to Pancreatic Triglyceride Levels: Pilot Investigation

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Abstract

Aims: Type 2 diabetes is a progressive disease and highly prevalent in Hispanic and Black minorities in the United States. Our research suggested that Black, compared to Hispanic and non-Hispanic White accumulate less of triglyceride within pancreatic tissue. Herein we describe ethnicity specific aspects of the relationship between pancreatic TG levels and beta cell function.

Methods: We studied 68 women: 16 Black, 26 Hispanic and 26 non-Hispanic White. We assessed insulin secretion and insulin sensitivity using frequently sampled glucose tolerance test - FSIVGTT, abdominal fat distribution using magnetic resonance imaging - MRI, and pancreatic triglyceride levels using proton magnetic resonance spectroscopy - ^{1}H MRS.

Results: Characteristics and results were similar for non-Hispanic White and Hispanic women, hence, we considered White and Hispanic as one group. In Hispanic/White pancreatic TGs were low in lean, elevated in obese and highest in type 2 diabetes. Beta-cell function, measured as a disposition index was lower in obese compared to lean and lowest in type 2 diabetes. Furthermore, pancreatic triglyceride (pTG) and the disposition index (DI) were inversely correlated: $DI = \frac{251}{pTG} + 660$, R^2=0.4099.

In non-Hispanic Black pancreatic triglyceride content was lower than in Hispanic/White, lowest in lean and marginally elevated in obese and type 2 diabetes. Beta cell function was low/normal in lean, significantly augmented in obese and reduced in type 2 diabetes. Unlike in Hispanic/White, in Blacks beta cell function expressed by DI was linearly proportional to pTG content: *DI= 328*pTG + 430*, R^2=0.4472.

Conclusions: The results of this research suggest an ethnicity specific relationship of beta-cell function and pTG content. In Hispanics/Whites, high pancreatic TG levels potentially represent the risk factor for beta-cell failure. In obese Blacks however, hypersensitivity of beta-cell to elevated pTGs and subsequent exaggerated glucose stimulated insulin secretion may represent the ultimate risk factor for the future advance to beta-cell failure.

Introduction

Obesity is the largest non-communicable global health problem of this century. It is associated with metabolic complications, risk factors for cardiovascular disease, insulin resistance, dyslipidemia, and much more. The very origin of metabolic deregulations in obesity is the thermodynamic imbalance between nutritional energy intake and energy expenditure [1]. Energy surplus is associated with increased deposits of triglyceride (TGs) in adipose as well as non-adipose tissues. These ectopic TGs constitute a rich source of free fatty acids (FFA) and derived metabolites such as diacylglycerol and ceramide which are toxic and obstruct pathways controlling insulin sensitivity and insulin secretion. The metabolic toxicity of FFA derived metabolites has been well documented in a variety of animal models [2-5], but it still has to be confirmed in humans. In humans, ectopic fat accumulation discriminates between metabolically healthy and metabolically abnormal obesity [5-12] in that the presence of high levels of ectopic fat in organs is associated with lipotoxic organ dysfunction [7,9].

When localized proton magnetic resonance spectroscopy (^{1}H MRS) became available to measure ectopic TG levels (TGs) within the pancreas, ectopic fat accumulation in pancreas and its relation to pancreatic beta-cell function became a strong focus of research in many labs [6,11-15], including our lab [10,16-18]. We use parenchymal pancreatic TG levels as a surrogate measure of TG levels in beta-cells. Prior to adopting this assumption, we demonstrated that TGs measured by ^{1}H MRS in the whole pancreatic tissue and levels of TGs in beta-cells isolated from the same pancreas by biochemical assay correlate well [19]. Although a direct correlation of pancreatic TGs and beta-cell dysfunction has been firmly demonstrated in animals, it is still contentious in humans as contradictory results from cross-sectional studies have been published [10,15,20,21]. However, reports by Taylor [11] invigorated the interest in the lipotoxic beta-cell dysfunction in humans [5,11,12,22]. In this longitudinal study Taylor [11] showed that during drastic calorie restriction for 12 weeks, pancreatic TGs were reduced and beta-cell function improved. These findings are in agreement with our previous results from a multi-ethnic population, showing that pancreatic TGs are associated with glucose stimulated insulin secretion [23]. In the present study, we hypothesized that pancreatic TG levels directly predict beta-cell function, measured as a disposition index (DI),which is defined as a product of glucose stimulated insulin secretion (AIR_g) and prevalent insulin sensitivity (SI): $DI=AIR_g*SI$. We further hypothesized that the

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relationship between pancreatic TG levels and beta-cell function is ethnicity specific [24,25].

Methods

Study population

We studied 68 women who self-reported race (Black or White) and ethnicity (Hispanic or non-Hispanic): 16 non-Hispanic Black, 26 non-Hispanic White, and 26 Hispanic. Study subjects in each race/ethnicity were divided into metabolic sub-groups: 1) lean (BMI <25 kg/m^2, fasting blood glucose <100 mg/dl (<5.55 mmol/dl), 2) overweight and obese (BMI ≥ 25 kg/m^2, fasting blood glucose <125 mg/dl (<6.94 mmol/dl) and 3) with type 2 diabetes –t2d (fasting blood glucose ≥125 mg/dl (≥ 6.94 mmol/dl) regardless of BMI. We adopted the following exclusion criteria: males (to avoid any possible gender confounding factors on abdominal and ectopic fat distribution); hypertension (blood pressure >140/85 mmHg or using blood pressure lowering medications); use of medication known to alter lipid metabolism (e.g., steroids, pioglitazone, metformin); subjective weight loss within six months prior to study; history of pancreatic or liver disorders; daily consumption of more than two alcoholic beverages; and contraindications to magnetic resonance imaging (metallic implants, claustrophobia, pregnancy, body weight more than 160 kg, or body circumference close to or exceeding the magnet bore size).

Study design

Each study subject completed three visits scheduled within three weeks. The initial screening visit was for consent and anthropometric assessment. Height and weight measurements were obtained from barefoot subjects wearing a standard hospital gown. Blood pressure was measured with a standardized protocol using a validated oscillometric monitor [26]. The second visit was for the frequently sampled intravenous glucose tolerance test (FSIVGTT) to measure insulin sensitivity, insulin secretion, and to calculate the disposition index. The final visit was for pancreatic TGs measurements using localized proton magnetic resonance spectroscopy (^{1}HMRS) and for abdominal fat distribution measurements using abdominal MRI. All experimental protocols were approved by Institutional Review Boards at Cedars-Sinai Medical Center and University of Texas Southwestern Medical Center. All participants signed consent to participation prior to the study.

		Lean	Obese	T2D
Age, years	**W/H**	37 ± 4	42 ± 2	53 ± 2*
	B	35 ± 10	39	43 ± 5
	p	**ns**	**ns**	**ns**
BMI, kg/m^2	**W/H**	21.1 ± 0.8*	33.5 ± 11	34.4 ± 1.7
	B	24.2 ± 0.7*	37.5 ± 2.5	38.8 ± 2.3
	p	**ns**	**ns**	**ns**
HbA1c, %	**W/H**	5.36 ± 0.11	5.43 ± 0.05	7.98 ± 1.27
	B	5.65 ±0.15	5.50 ± 0.12	7.53 ± 0.73
	p	**ns**	**ns**	**ns**
Leptin, ng/ml	**W/H**	9 ± 2*	43 ± 4	30 ± 5
	B	16 ± 4	73 ± 15	26 ± 5
	p	**ns**	**p<0.05**	**ns**
Adiponectin, ng/ml	**W/H**	14 ± 2*	9 ± 1	9 ± 2
	B	9 ± 1	9 ± 1	8 ± 2
	p	**ns**	**ns**	**ns**
Cholesterol, mg/dL	**W/H**	153 ± 9	177 ± 6	193 ± 7
	B	177 ± 22	174 ± 7	140 ± 9
	p	**ns**	**ns**	**p<0.05**
LDL, mg/dL	**W/H**	86 ± 6	108 ± 5	116 ± 8
	B	111 ± 19	102 ± 19	82 ± 8
	p	**ns**	**ns**	**p<0.05**
HDL, mg/dL	**W/H**	54 ± 3	44 ± 2	45 ± 7
	B	51 ± 0	48 ± 7	40 ± 3
	p	**ns**	**ns**	**ns**

Data shown as mean ± SE; * p<0.05 in Hispanic/White or in in Blacks;
p- statistical significance between Hispanic/Whites and Blacks
HbA1c: Hemoglobin A1c; LDL: Low Density Cholesterol; HDL: High Density Cholesterol; pTG: Pancreatic Triglyceride; AIRg: Glucose Stimulated Insulin Response; DI: Disposition Index; SI: Insulin Sensitivity

Table 1a: Metabolic characteristics of study subjects.

FSIVGTT

FSIVGTT was performed at 8:30 A.M. after an overnight fast. Two intravenous polyethylene catheters were inserted into antecubital veins, one for infusion of glucose and regular human insulin and the other for blood sampling. A bolus of 50% glucose solution (0.3g glucose/kg body weight) was injected at time 0, and a bolus of regular human insulin (0.03 units/kg body weight) was injected 20 minutes later. Blood samples were collected for determination of plasma glucose and insulin levels at -15, -10, -5, -1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 minutes. Data were analyzed using the Millennium Minimal Model software [27]. Glucose stimulated insulin secretion (acute insulin response to glucose (AIR_g)) describing first-phase insulin secretion was calculated from the first 10 min after the intravenous glucose bolus. The disposition index (DI), which is the product of AIR_g and insulin sensitivity (SI),

$DI = AIR_g * SI$, was used to estimate beta-cell function.

^{1}H MRS

Pancreatic TGs were quantified in vivo using ^{1}H MRS at 1.5 Tesla as previously described [10,21]. In brief, high resolution, perpendicular images through the abdomen were collected to locate the pancreas. Images were acquired with breath-hold at the end of exhalation. The volume for spectroscopic testing (2 ml) was selected with special attention not to include visceral fat in the volume of interest. Spectroscopic data were collected as volunteers breathed freely with utilization of PACE (**P**rospective **A**cquisition **C**orr**E**ction) respiratory motion compensation and with ^{1}H MRS signal acquisition triggered at exhalation. Data were acquired and processed as previously described [10,21].

Abdominal magnetic resonance imaging

The amount of subcutaneous and visceral abdominal fat was determined from a single abdominal axial image at the level between the vertebral L2 and L3 bodies [28]. Image analysis was performed by a single observer blinded to the volunteer's characteristics using Slice-O-Matic software (4.3 rev 10; Virtual Magic Inc., Montreal, Canada).

Biochemical analyses

Plasma glucose, plasma TGs, cholesterol and HDL cholesterol, alanine transaminase, and aspartate transaminase concentrations were determined by enzymatic calorimetric assays using a Chemistry Analyzer Model ATAC 8000 (Elan Diagnostic Co., Brea, CA) [29]. LDL cholesterol levels were calculated using the Friedewald equation [30]. Plasma insulin was quantified by a paramagnetic particle chemiluminescent immunoassay using the Beckman Immunoassay Systems Access II (Beckman Coulter, Inc., Chaska, MN).Baseline venous blood sampling was performed for measurement of lipid profile, hemoglobin A1c.

Statistical analysis

The statistical analysis was performed using Statgraphics Centurion XVI software. The evaluation of the differences among the groups (lean, overweight/obese and t2d) was performed using one-way ANOVA for each ethnic group under consideration with Fisher's least significant difference (LSD) procedure to discriminate which differences are significant. For each group, the comparison between ethnicities (Tables 1A and1B) was performed using the t-test. The verification of no significant difference in distribution for both samples compared was performed using the Kolmogorov-Smirnov test. The models for DI were estimated with linear regression versus 1/pTG and pTG for Whites/Hispanics and Blacks respectively.

Results

Characteristics of race/ethnic study groups

The demographic characteristics and results were similar for non-Hispanic White and Hispanic women (age: p=0.06, BMI: p=0.82, sub-cutaneous fat: p=0.69, visceral fat: p=0.58 as well as pancreatic TGs: p=0.88); hence, we considered White and Hispanic women as one group (Hispanic/White). Throughout the rest of this manuscript ethnicity/race categories are referred to as Hispanic/White and Black. Demographic and metabolic characteristics by ethnicity and metabolic subgroups are listed in Tables 1A and 1B. The metabolic sub-groups were defined as: 1) lean; 2) overweight and obese (obese), 3) type 2 diabetes (t2d). Lean Hispanic/White had BMI not different from lean Blacks. Obese Blacks had higher BMI than obese Hispanic/White. Black and Hispanic/White with t2d had comparable BMI. HbA1c values were similar in lean, obese, and were higher in type 2 diabetes. Overall, obese Blacks had higher leptin levels, Blacks with type 2 diabetes had lower cholesterol and LDL compared to Hispanics/Whites with type 2 diabetes.

Abdominal fat distribution

Visceral fat: Visceral fat was the lowest in lean and significantly different between lean Hispanic/White and lean Black (42 ± 7 cm^2 versus 86 ± 15 cm^2, p<0.05). In obese and t2d Hispanic/White amount of visceral fat increased significantly compared to lean, tri-fold in obese and four-fold in type 2 diabetes (143 ± 11 cm^2 and 172 ± 17 cm^2 respectively). However, in Black amount of visceral fat increased only 0.5 fold in obese and type 2 diabetes (121 ± 6 cm^2 and 127 ± 23 cm^2 respectively) and was not significant.

Subcutaneous fat: Subcutaneous fat was the lowest in lean and significantly different between lean Hispanic/White and lean Black (87 ± 15 cm^2 versus 155 ± 8cm^2, p<0.05). In obese and t2d Hispanic/White and Black amount of subcutaneous fat increased tri-fold. (Obese Hispanic/Whites 305 ± 28cm^2; t2d Hispanic/White 259 ± 31cm^2 versus obese Black 473± 74 cm^2 and t2d 419 ± 95 cm^2 respectively).

Relationship between Disposition Index and pancreatic TG levels

Hispanic/White: Pancreatic TG (pTG) levels were lowest in lean (0.96 ± 0.46 %) and elevated in obese (5.22 ± 0.88 %). In t2d, pancreatic TGs were significantly higher compared to lean (pTG=13.26 ± 3.35%), (Figure 1A).

Insulin sensitivity (SI) was highest in lean (SI=8.31 ± 1.12 *L/(mU*min)* versus other groups. SI was lower in the obese and t2d groups (SI=3.28 ± 0.26 *L/(mU*min* and SI=1.93 ± 0.59 *L/(mU*min* respectively) (Figure 1B).

Glucose stimulated insulin secretion (AIR_g) was significantly higher in obese vs lean (AIR_g=367 ± 29 *mU*min/L*vs204 ± 78 *mU*min/L*) and was decreased int2d (AIR_g=98 ± 49 *mU*min/L*) (Figure 1C).

Disposition Index (DI), a strong predictor of progression to t2d, was similar between lean (1312 ± 265) and obese (1088 ± 185), and decreased in t2d (125 ± 55) (Figure 1D).

In the entire studied Hispanic/White population, pancreatic TG levels and DI were inversely correlated and described with a specific equation $DI = 660 + 251/pTG$, R^2=0.4099, p<0.00001, (Figure 2A). The relationship between DI and pancreatic TGs remained significant after adjusting for BMI and abdominal (subcutaneous and visceral) fat.

		lean	obese	T2D
Subcutaneous fat, cm^2	**W/H**	87 ± 15*	305 ± 29	259 ± 31
	B	155 ± 8	473 ± 74	419 ± 95
	p	**ns**	**p<0.05**	**ns**
Visceral fat, cm^2	**W/H**	42 ± 7*	143 ± 13	172 ± 17
	B	86 ± 15	121 ± 6	127 ± 23
	p	**p<0.05**	**ns**	**ns**
pTG, f/w %	**W/H**	0.96 ± 0.43	5.22 ± 0.88	13.26 ± 3.35*
	B	0.48 ± 0.28	3.79 ± 0.90	1.77 ± 0.73
	p	**ns**	**ns**	**p<0.05**
AIR_g, mU*min/L	**W/H**	204 ± 78	367 ± 29*	98 ± 49
	B	161 ± 73	1353 ± 326	613 ± 328
	p	**ns**	**p<0.05**	**ns**
DI	**W/H**	1312 ± 265	1088 ± 116	125 ± 55*
	B	652 ± 249	2057 ± 367*	321 ± 134
	p	**ns**	**p<0.05**	**ns**
SI, L/(mU*min)	**W/H**	831 ± 1.13*	3.28 ± 0.26	1.93 ± 0.59
	B	4.20 ± 0.35*	1.88 ± 0.38	1.23 ± 0.34
	p	**ns**	**p<0.05**	**ns**

Data shown as mean ± SE; * p<0.05 in Hispanic/White or in in Blacks;
p- statistical significance between Hispanic/Whites and Blacks
HbA1c: Hemoglobin A1c; LDL: Low Density Cholesterol; HDL: High Density Cholesterol; pTG: Pancreatic Triglyceride; AIRg: Glucose Stimulated Insulin Response; DI: Disposition Index; SI: Insulin Sensitivity

Table 1b: Results.

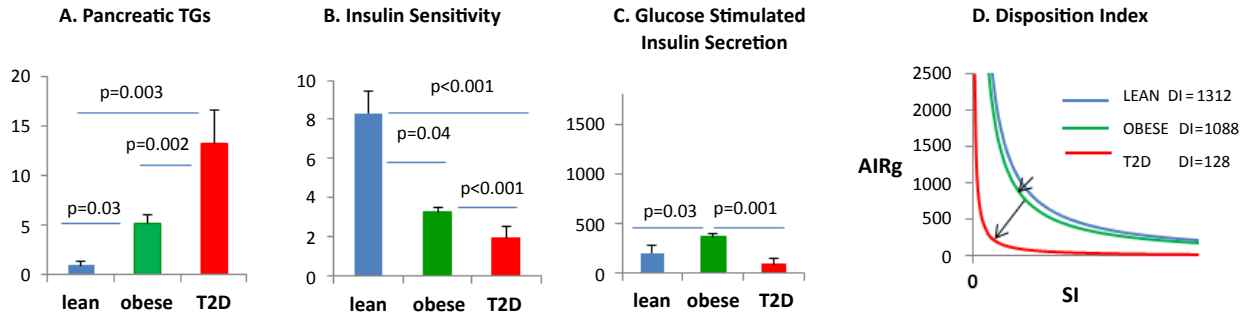

Figure 1: Pancreatic TG levels and beta cell function by metabolic subgroups in Hispanic/White.

Panel A – Pancreatic TG (pTG); Panel B – Insulin Sensitivity (SI); Panel C – Glucose stimulated insulin secretion (AIR_g); Panel D – Disposition Index DI=SI* AIR_g. Specific p values marking significant differences between metabolic groups are indicated (in cases of p<0.05).

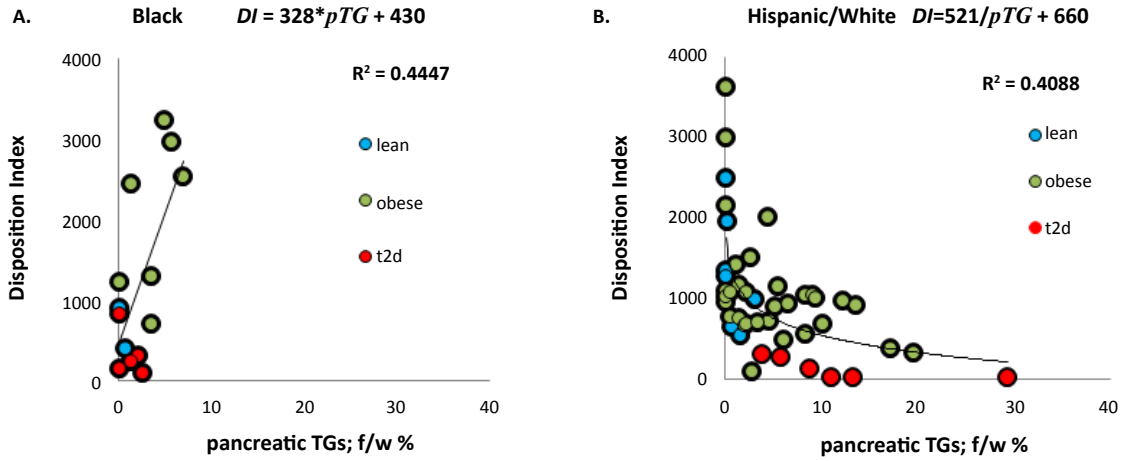

Figure 2: Relationship of disposition index (DI) and pancreatic TG levels (pTG)

Panel A - In Black women disposition index is in a linear - proportional relationship with pancreatic TG levels. Panel B - In Hispanic / White women disposition index is in nonlinear - inverse relationship with with pancreatic TG levels.

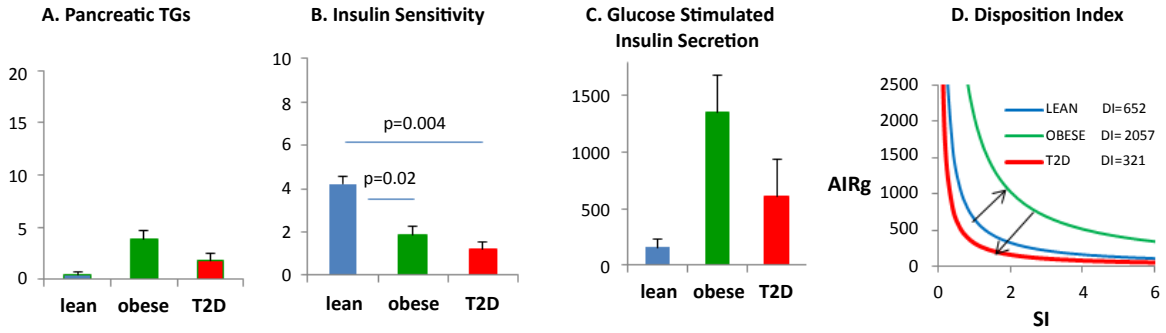

Figure 3: Pancreatic TG levels and beta cell function by metabolic subgroups in Blacks

Panel A – Pancreatic TG (pTG); Panel B – Insulin Sensitivity (SI); Panel C – Glucose stimulated insulin secretion (AIR_g); Panel D – Disposition Index DI=SI* AIR_g. Specific p values marking significant differences between metabolic groups are indicated (in cases of p<0.05).

Blacks: Pancreatic TGs were lower in obese and t2d Blacks than in obese and t2d Hispanic/White. In Blacks pancreatic TG levels were lowest in lean (0.96 ± 0.46 %) and elevated in obese (3.45 ± 0.68 %) and t2d (1.77 ± 0.73%), (Figure 3A).

Insulin sensitivity (SI) was in general lower in Blacks than in Hispanics/Whites across all metabolic groups. SI was highest in lean Black (SI=4.20 ± 0.35 units) and was lower in obese (1.88 ± 0.38) and t2d (1.23 ± 0.34), (Figure 3B). Glucose stimulated insulin secretion

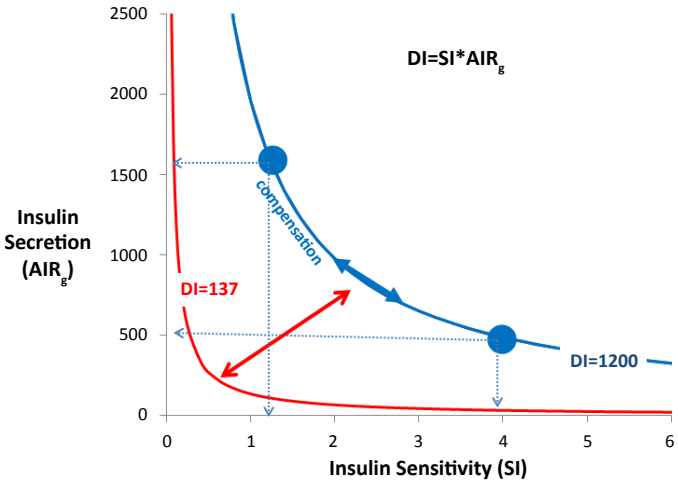

Figure 4: The concept of a hyperbolic Disposition Index as a predictor of progression to t2d

DI is defined as a product of SI and AIR$_g$, DI=SI* AIR$_g$ and is illustrated as a two dimensional hyperbola with AIRg as an ordinate and SI as an abscissa. The hyperbolic relationship between SI and AIR$_g$ allows for the small changes in any component to be compensated by small changes in the other component for the hyperbola value to stay constant i.e. small changes in SI are compensated by the AIRg or vice versa - blue line. An adequate compensatory change result in a constant hyperbola, however, the worsening compensation will result in lowering of DI value and will indicate a progression to t2d – red line. Improvement of the either component beyond compensation will lead to higher DI value indicating metabolic improvement (27 and references within).

(AIR$_g$) higher in obese Black compared to obese Hispanic/White. In Black glucose stimulated insulin secretion (AIR$_g$) was lowest in lean, higher in obese (p=0.05), and diminished in t2d, (Figure 3C). The pattern of Disposition Index (DI) across Black metabolic sub-groups was different from the pattern in Hispanic/White sub-groups: lowest in lean, exaggerated in obese, and drastically diminished in t2d, (Figure 3D).

Unlike in Hispanic/White, in the Black population pancreatic TG levels and DI were linearly correlated and described with a specific equation *DI= 328*pTG + 430*, R^2=0.4472, p=0.006, (Figure 2B). This relationship between pancreatic TG levels and disposition index remained significant after adjusting for BMI and abdominal (visceral and sub-cutaneous) fat distribution.

Discussion

In a multi-ethnic population of women with a broad range of glucose control, from normal to type 2 diabetes, we studied the relationship between beta-cell function and triglyceride levels within pancreatic tissue. Our major new observations include specific ethnic difference in pancreatic fat distribution and associated beta-cell function between obese Hispanic/White and obese Black. Small elevation of pancreatic TGs in obese Black was associated with massively amplified DI while a significant increase of pancreatic TGs in obese Hispanic/Whites was associated with decreased DI. Our important new finding is that in Blacks the disposition index and pancreatic TGs are linearly proportional, suggesting stimulation of beta-cell function with marginally increased pancreatic TGs. On the contrary, in Hispanic/White the DI and pancreatic TGs are in inverse relationship, suggesting beta-cell function impairment with elevation of pancreatic TGs. Altogether, our results suggest that mechanisms responsible for beta-cell function in Blacks versus Hispanics/Whites may vary. Just elevated pancreatic TG levels in Blacks and high pancreatic TG levels in Hispanics/Whites may result in specific interactions/communications of FFA and beta-cells function reflected in the value of the disposition index, a potent predictor of a progression to t2d. DI is defined as a product of SI and AIRg, DI=SI*AIRg, and it is graphically illustrated as a two dimensional hyperbola with AIR$_g$ as an ordinate and SI as an abscissa. The hyperbolic relationship between two components allows for the small changes in any component to be compensated/adjusted by changes in the other component for the hyperbola value to stay constant. In case of DI hyperbola, small changes in SI are compensated by the AIR$_g$ or vice versa, as indicated by blue line in figure 4. An adequate compensation results in a constant DI, but worsening compensation results in lowering of DI value and indicates metabolic progression to t2d, (Figure 4). In case of treatment, improvement of either component beyond the compensation results in higher DI value indicating metabolic improvement. Our results in Hispanic/White population clearly fit to this model. Our results in Black population seem confusing at the first glance. DI in obese Black is significantly higher compared to lean Black suggesting that metabolism of obese Black is superior to metabolism of lean Black. However, considering DI and pancreatic TGs for Black and Hispanic/White, our results seem rather to suggest ethnicity specific pathways of natural history of type 2 diabetes. High and low levels of fat in the pancreas may differently contribute to the pathogenesis of type 2 diabetes as different concentrations of fatty acids and their derivates may differently interact with insulin signaling and insulin secretion [11,31]. Under normal metabolic conditions, adipose tissue serves as a buffer for the influx of the dietary fat into the circulation. This seems to be confirmed by higher amount of subcutaneous fat in Black compared to Hispanic/White. In vitro and in vivo studies demonstrated that FFAs exert a dual action on insulin secretion [8,32-34]. Glucose stimulated insulin secretion is increased in response to raised plasma FFA during intra lipid infusion in humans [8,33]. In contrast, chronic exposure of beta-cell to high levels of FFA attenuates markedly glucose stimulated insulin secretion and additionally increases insulin secretion in response to low glucose levels. In light of this evidence, it is logical to consider a dual response of β-cell function to FFA to explain observed difference in the natural history of type 2 diabetes in Blacks and in Hispanic/White. We suggest the analogy of short term exposure of beta-cell to FFA for the explanation of metabolic changes in Black, and the

analogy of chronic exposure of beta-cell to FFA in Hispanics/Whites. This explanation harmonizes with the lipotoxicity hypothesis [9,10,33]. Using the lipotoxicity hypothesis convention, we assume that in Blacks, subcutaneous adipose tissue has preserved fat storage function, which prevents ectopic fat spill-over. Blacks have more subcutaneous fat and less visceral and ectopic fat compared to Hispanic/White. Mild elevation of pancreatic TGs, even within normal range, significantly enhances glucose stimulated insulin secretion in this population (Figure 2A). In Hispanics/Whites, who have less subcutaneous fat and more visceral and ectopic fat, there seems to be a predilection towards ectopic fat deposition and FFA lipotoxic damage to pancreatic beta-cell function. In Hispanics/Whites pancreatic TGs are high overall and in inverse relationship with beta-cell function (Figure 2B).

Other factors, such as a different genetic makeup in Blacks and Hispanics/Whites and/or individual genetic lipo-susceptibility may further enhance these ethnic differences [35,36].

Genetic studies by the SIGMA Consortium [37] have identified a novel locus associated with type 2 diabetes at genome-wide significance - SLC16A11-. The risk for t2d was present at 50% frequency in Native Americans and was rare in African. Importantly, expression of SLC16A11 in cells alters lipid metabolism, most notably causing an increase in intracellular triacylglycerol. These findings strongly support our hypothesis of ethnicity specific beta cell function due to different levels of intra-pancreatic triglyceride.

Our results are also in agreement with conclusions of recent systematic review and meta-analysis of ethnic differences in relationship between insulin sensitivity and glucose stimulated insulin secretion [38]. This systematic analysis included 3,813 individuals in three major ethnic groups: Blacks (19 cohorts), Whites (31 cohorts), and East Asians (24 cohorts). Similar to our results, non-diabetic Blacks compared to non-diabetic Whites had lower insulin sensitivity and much higher glucose stimulated insulin secretion. The authors concluded that perhaps the difference in t2d pathogenesis is evolutionary and perhaps Blacks have evolved to develop robust β-cell function, to maintain normo-glycemia despite of relatively low insulin sensitivity, and perhaps Whites have evolved to be relatively insulin sensitive and thus developed less robust β-cells which have limited capability to increase insulin secretion when needed [38].

Our study is not limitations free. We studied exclusively women to avoid confounding from gender differences in abdominal and ectopic fat distribution. In this in vivo study, we used the levels of TG within pancreatic tissue as a surrogate for TG levels within beta-cells. However, we have demonstrated previously that pancreatic TG levels in vivo closely mimic levels of TGs in beta cells and thus are good, and the only thus far *in vivo*, surrogate measure of TGs in beta-cells [20]. The number of Black participants in this study was lower than the number of participants in other ethnicities. However, in prior studies, using larger population based cohorts we reported that Black populations had similar low ectopic fat distribution [10,18], consistent with our current findings, albeit with a much smaller sample size. Our results are also consistent with findings by others that Black women have higher AIR_g compared to White women [39]. We were able to minimize the theoretical issue of confounding variables by studying a relatively young population and including newly diagnosed type 2 diabetes patients. Our results clearly demonstrate correlation between pancreatic TG levels and beta cell function which carries a significant ethnicity/race component and fits well with previous findings [39].

In conclusion, our results suggest ethnic differences in development of beta cell dysfunction and that pancreatic TGs predict ethnicity specific beta cell dysfunction. In Hispanics/Whites, high pancreatic TG levels may represent the potential risk factor for beta-cell failure. In obese Blacks, however, hypersensitivity of beta-cell to elevated pancreatic TGs and subsequent exaggerated glucose stimulated insulin secretion may represent the ultimate risk factor for the future advance to beta-cell failure. These observations need confirmation by studies across both genders and including other ethnicities. If confirmed, these observations may inspire development of ethnicity specific therapies for beta-cell dysfunction and for ethnicity specific t2d treatments.

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IL participated in study design, performed experiments, researched and analyzed data, and contributed to writing the manuscript. RM performed experiments, contributed to discussion and reviewed manuscript. EWS performed experiments, post-processed and analyzed data including statistics, reviewed data, and contributed to discussion. LSS designed the study, researched and analyzed data, and wrote the manuscript. LSS is a guarantor of this work, and as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

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