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From Prediabetes to Type 2 diabetes in Obese Youth: Pathophysiological Characteristics Along the Spectrum of Glucose Dysregulation.

Abbreviated Title: Impaired glucose regulation in obese youth**.**

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Objective: Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are considered prediabetic states. There are limited data in pediatrics in regards to their pathophysiology. We investigated differences in insulin sensitivity (IS) and secretion among youth with IFG, IGT, and coexistent IFG/IGT compared to normal glucose tolerance (NGT) and type 2 diabetes (T2DM).

Research Design and Methods: 24 NGT, 13 IFG, 29 IGT, 11 IFG/IGT and 30 T2DM obese adolescents underwent evaluation of hepatic glucose production [6,6-$^{2}H_2$ glucose], insulin stimulated glucose disposal (Rd-euglycemic clamp), 1st and 2nd phase insulin (1stPI, 2ndPI) secretion (hyperglycemic clamp); body composition (DEXA), abdominal adiposity (CT) and substrate oxidation (indirect calorimetry).

Results: NGT, prediabetes and T2DM adolescents had similar body composition and abdominal fat distribution. Rd was lower (p=0.009) in T2DM vs NGT. Compared with NGT, 1st PI was lower in IFG, IGT and IFG/IGT with further deterioration in T2DM, p<0.001. Compared with NGT, β-cell function relative to insulin sensitivity (glucose disposition index or GDI) was lower in IFG, IGT, and IFG/IGT (40%, 47% and 47% respectively), with further decrease (80%) in T2DM, p<0.001. GDI was the major determinant of fasting and 2-hr glucose level.

Conclusions: Obese adolescents who show signs of glucose dysregulation, including abnormal fasting glucose, glucose intolerance or both, are more likely to have impaired insulin secretion than reduced insulin sensitivity. Given the impairment in insulin secretion, they are at high risk for progression to type 2 diabetes. Further deterioration in insulin sensitivity or secretion may enhance the risk for this progression.

Prediabetes, defined as the presence of elevated fasting glucose, abnormal glucose tolerance or both, is associated with an enhanced risk for development of type 2 diabetes in adults (1), but there are limited data to define the significance in children. A recent change in the definition of the abnormal fasting glucose to a lower level (100-125 mg/dl) has increased the prevalence of prediabetes in both adults and youth (2-4). It is unclear from the literature what role a defect in insulin secretion or an abnormality of insulin sensitivity might play in the impairment of glucose regulation leading to glucose intolerance or elevated fasting plasma glucose.

Epidemiological studies suggest that subjects with impaired fasting glucose have lower insulin sensitivity and higher insulin secretion (5,6) based largely on fasting indices of insulin sensitivity and oral glucose tolerance (OGTT)-derived single index of insulin secretion (5). Adult studies reveal similar or lower insulin sensitivity in subjects with impaired glucose tolerance compared with those with impaired fasting glucose who have lower insulin secretion (7,8). These studies are contrasted with clamp studies in Pima Indians showing similar insulin sensitivity in subjects with impaired fasting glucose and impaired glucose tolerance but lower insulin secretion in those with fasting dysglycemia (9).

Pediatric data are limited. In overweight Latino children with a family history of type 2 diabetes (10), children with impaired vs normal fasting glucose, had no significant differences in insulin sensitivity or acute

insulin response. However, glucose disposition index (GDI), or insulin secretion relative to insulin sensitivity, was significantly reduced
(15% lower) in children with impaired fasting glucose. A more recent study in obese adolescents revealed that subjects with impaired fasting glucose had decreased glucose sensitivity of first phase insulin secretion and liver insulin sensitivity whereas those with impaired glucose tolerance had more severe degrees of peripheral insulin resistance compared with subjects with normal glucose tolerance (11). We recently demonstrated that insulin secretion relative to insulin sensitivity shows a significantly declining pattern: highest in youth with normal glucose tolerance, intermediate in those with impaired glucose tolerance, and lowest in youth with type 2 diabetes (12).
In an attempt to clarify the controversy concerning the metabolic derangements in the different categories of the prediabetes state, the present study aimed: 1) to investigate the metabolic characteristics of insulin sensitivity and secretion in obese youth, with impaired fasting glucose vs impaired glucose tolerance, of similar body composition and abdominal adiposity, and 2) to compare them not only to those with normal glucose tolerance but also to children with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Population: Twenty four obese adolescents with normal glucose tolerance (NGT), 13 with impaired fasting glucose (IFG), 29 with impaired glucose tolerance (IGT), 11 with combined IFG/IGT and 30 with type 2 diabetes (T2DM), African American (AA, n=45) and American White (AW, n=62) adolescents were studied. IFG was defined according to the 2003 ADA guidelines as a fasting plasma glucose (FPG) of $\geq$100-125 mg/dl (13), based on the average of 2 fasting glucose measurements at the time of the OGTT (at –15 and 0 minutes) or the average of 7 fasting glucose measurements obtained during the 2 clamp procedures (3 samples every 15 minutes at the baseline of the hyperglycemic clamp and 4 samples every 10 minutes at the baseline of the euglycemic clamp) and normal glucose tolerance with 2hr post OGTT glucose of <140 mg/dl. IGT was defined as normal FPG <100 mg/dl and 2-hr post OGTT glucose of $\geq$140-199 mg/dl according to ADA criteria (13). Combined IFG/IGT had FPG $\geq$100-125 mg/dl and 2hr glucose between $\geq$140-199 mg/dl (13). All subjects were pubertal, had exogenous obesity with no clinical evidence of endocrinopathy associated with obesity. They were not involved in any regular physical activity or weight reduction programs. The adolescents with type 2 diabetes were clinically diagnosed according to ADA and WHO criteria (14), and were negative for glutamic acid decarboxylase (GAD) and insulinoma associated protein-2 autoantibody (IA2 Ab). T2DM subjects were on treatment with lifestyle alone (n= 7), metformin (n= 11), metformin +insulin (n= 10) or insulin alone (n= 2). All other participants were not on any medications that affect glucose metabolism. In type 2 diabetes, metformin and long acting insulin were discontinued 48 hrs before the clamp studies. Some of the participants (12 NGT, 19 IGT and 17 with type 2 diabetes) have been reported before (12). All studies were approved by the Institutional Review Board of the University of Pittsburgh. Informed consent was obtained. Clinical characteristics of the study subjects are summarized in Table 1.
Clamp Studies. Participants were admitted twice within a 1-3 week period to the Pediatric Clinical and Translational Research Center (PCTRC) the day before the clamp studies, once for a hyperinsulinemic-euglycemic clamp and the other time for a hyperglycemic clamp in random order. The 2-hr OGTT (1.75 g/kg of glucola (max 75 g))

was performed the day prior to the first PCTRC admission.

In-vivo insulin stimulated glucose disposal. A fasting blood sample was obtained for determination of cholesterol, LDL, HDL, VLDL, TG, HbA1c, proinsulin and C-peptide. Fasting endogenous glucose production was measured with a primed constant rate infusion of [6,6-$^2H_2$] glucose (0.306±0.009 μmol/kg/min) (Isotech, Miamisburg, OH) (12). Insulin-mediated glucose metabolism (Rd) and insulin sensitivity were evaluated during a 3-h hyperinsulinemic-euglycemic clamp (12). Continuous indirect calorimetry by a ventilated hood (Deltatrac Metabolic Monitor, Sensormedics, Anaheim, CA) was used to measure CO2 production, O2 consumption and respiratory quotient (RQ). Measurements were made for 30 minutes at baseline and at the end of the euglycemic clamp (12).

In-vivo insulin secretion. First and second phase insulin and C-peptide secretion was evaluated during a 2-h hyperglycemic clamp (12.5 mmol/l) as before (12).

Body Composition. Body composition was determined by DEXA, and subcutaneous abdominal adipose tissue (SAT) and visceral adipose tissue (VAT) by a single slice CT scan at L_4-L_5 (12).

Biochemical Measurements. Plasma glucose was measured with a glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, Ohio), insulin and C-peptide by radioimmunoassay (RIA) as before (12). HbA1c was measured by high performance liquid chromatography (Tosoh Medics, Inc. 1998) and lipids using the standards of the Centers for Disease Control and Prevention (12). Deuterium enrichment of glucose in the plasma was determined on a Hewlett-Packard Co. 5973 mass spectrometer (Palo Alto, CA) coupled to a 6890 gas chromatograph (12). Pancreatic autoantibodies were determined in the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington (Seattle, WA) using the NIDDK-sponsored standardization assay.

Calculations: Fasting hepatic glucose production (HGP) was calculated during the last 30 min of the 2-hr isotope infusion according to steady-state tracer dilution equations (12). In the fasting state, an index of hepatic insulin resistance was calculated as the product of HGP and fasting insulin levels (14). Insulin stimulated glucose disposal rate (Rd) was calculated during the last 30 minutes of the euglycemic clamp to be equal to the rate of exogenous glucose infusion and expressed per fat free mass (mg/min/Kg FFM). Peripheral insulin sensitivity was calculated by dividing the Rd by the steady-state clamp insulin level and expressed per FFM (mg/min/FFM per μu/ml) (12). Insulin-stimulated carbohydrate oxidation rates were calculated according to the formulas of Frayn (12).

During the hyperglycemic clamp, the first and second phase insulin and C-peptide concentrations were calculated as described previously (12). Glucose disposition index (GDI) was calculated as the product of insulin sensitivity x 1st phase insulin and expressed as mg/min/kg FFM.

Statistics: Statistical analyses were performed using ANOVA followed by post-hoc Bonferroni correction for five group comparisons. Kruskal-Wallis test was used for multiple group comparison of non-parametric variables and chi-square to evaluate categorical variables. Spearman's correlation and multiple regression analyses were used to evaluate bivariate and multivariate relationships, respectively. Non parametric variables were log transformed for the regression analyses. Data are presented as mean±SD. Two-tailed $p \leq 0.05$ was considered statistically significant.

RESULTS

Study Subjects and fasting metabolic profile (Table 1). Table 1 depicts

characteristics of the 5 groups of obese adolescents with normal glucose tolerant (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), combined (IFG/IGT), and type 2 diabetes (T2DM). There were no significant differences in age, sex, tanner stage or ethnic distribution among the 5 groups. All subjects were pubertal. There were no significant differences in BMI, %body fat or abdominal visceral or subcutaneous fat among the 5 groups.

Fasting glucose was different among the groups as expected based on pre defined categorization. There was no difference in fasting insulin levels among the 5 groups. Fasting endogenous glucose production (HGP) was significantly higher in T2DM compared with the NGT group (post-hoc p=0.004) with no difference among the prediabetes groups. Postabsorptive hepatic insulin resistance tended to be higher in T2DM vs NGT (post hoc p=0.07) with no difference among the other prediabetes groups. Proinsulin/insulin ratio was higher in T2DM but not significantly higher in the prediabetes groups compared to NGT. Fasting lipid profile was not different among the groups (Table 1).

***In vivo* Insulin stimulated Glucose Disposal and Insulin Secretion (Figure 1).** Total, oxidative and non-oxidative glucose disposal were lower in type 2 diabetes compared with the NGT group. Oxidative glucose disposal was lower in T2DM compared with NGT (p=0.016), IFG (p=0.003), and IGT (p=0.023) in post hoc analysis but not different from IFG/IGT (Figure 1-A). First phase insulin levels were significantly lower in IFG (post hoc p=0.02), IGT (p=0.009), IFG/IGT (p=0.011) and lowest in T2DM (p<0.001) compared with the NGT group (Figure 1-B). Similarly, 1st phase C-peptide levels were lowest in T2DM and significantly different between T2DM and NGT (p<0.001). Second phase insulin (Figure 1-B) levels were significantly reduced in the T2DM compared with NGT (p<0.001) and compared with IGT (p=0.001) but not IFG (p=0.3) or IFG/IGT. GDI, which is insulin secretion relative to insulin sensitivity, was significantly impaired in all categories of prediabetes, lowest in T2DM and significantly different than IFG and IGT but not IFG/IGT (Figure 1-C). Youth with type 2 diabetes on different treatment modalities did not differ with respect to their peripheral glucose disposal, insulin secretion or glucose disposition index (data not shown).

Determinants of Fasting Glucose and Oral Glucose Tolerance (Figure 2). Fasting glucose correlated with hepatic insulin resistance (r= 0.30, p=0.004), 1st phase (r=-0.58, p<0.001), and 2nd phase (r=-0.47, p<0.001) insulin, and with GDI (r=-0.57, p<0.001) but not with peripheral insulin sensitivity. Similarly, 2-hr OGTT glucose correlated with 1st phase (r=-0.48, p<0.001), and 2nd phase (r=-0.40, p<0.001) insulin, and with GDI (r=-0.63, p<0.001) but not with insulin sensitivity. In a multiple regression analysis with age, gender, ethnicity, BMI, hepatic insulin resistance and GDI as independent variables and 2hr OGTT glucose or fasting glucose as the dependent variable, GDI was the significant determinant of the variance in the 2hr glucose (β=-.47, p<0.001) and the fasting glucose (β=-.32, p=0.009). With VAT or fat mass instead of BMI in the regression model, GDI remains the significant determinant of the variance in mean fasting glucose (β=-.4, p<0.001) and in 2 hr glucose (β=-.5, p<0.001). The relationship between GDI and 2hr OGTT glucose or fasting glucose is depicted in Figure 2.

DISCUSSION

In this study, we hypothesized that for similar degrees of adiposity insulin sensitivity will not differ among the different prediabetes groups compared with those with normal glucose tolerance but will be lower in youth with type 2 diabetes, while insulin secretion will be impaired in all categories of glucose

dysregualtion. Consistent with our hypothesis, the current findings demonstrate that all prediabetes states in obese youth, of similar BMI, %body fat and abdominal adiposity, are characterized by reductions in β-cell function relative to insulin sensitivity, with no difference in insulin sensitivity. In youth with impaired fasting glucose (IFG) compared with normal glucose tolerance (NGT), insulin stimulated glucose disposal is preserved whereas first and second phase insulin secretion is ~ 50 and 30% impaired. In youth with impaired glucose tolerance (IGT) compared with NGT first phase insulin is ~ 40 % lower with preservation of second phase insulin. When both defects, IFG and IGT coexist, the impairment in insulin secretion is a mixture of both with ~ 55% lower 1st phase insulin and 30% lower second phase. In the full blown picture of the diabetic state, insulin stimulated glucose disposal is impaired by ~ 30%, first phase insulin by ~ 75% and second phase by ~ 65% compared with NGT. Such cross sectional observations are consistent with longitudinal studies showing a higher risk of progression to T2DM in the combined IFG/IGT subjects compared with isolated impaired fasting glucose or impaired glucose tolerance (15).

The present study is confirmatory of some of the existing adult literature, but contradicts others. Our findings are consistent with observations in adults demonstrating greater impairment in insulin secretion in IFG (9, 14, 16, 17) compared with IGT, in that the defect in insulin secretion involves both 1st phase and second phase insulin in IFG whereas second phase insulin is preserved in IGT. Moreover, adult studies indicate that the loss of beta cell function may start at levels of fasting plasma glucose on the higher end of the conventional normal range (18). A recent longitudinal study suggests that a defect in insulin secretion (evaluated by OGTT derived index) is present in subjects with IFG and apparent 5 years before the development of fasting hyperglycemia (19). On the other hand, other investigations in adults show greater insulin resistance in impaired glucose tolerance (IGT) groups compared with IFG or NGT groups unlike our findings (17,18). However, a major contrast between our study and the adult studies, besides the age factor, is that almost invariably, the reported IGT (9,15,17,18,20) or IFG (9,15,18,20) adults have higher BMI and/or abdominal fat compared with the NGT groups, which could contribute to the observed differences in insulin action between IGT, IFG and NGT categories. This is supported by the fact that when subjects have similar anthropometric measures (21), investigators did not find significant differences in peripheral glucose uptake in IFG or IFG/IGT compared to the NGT group (21). Also, controlling for body composition (BMI and waist to hip ratio) eliminated differences in insulin sensitivity among NGT, IFG and IGT subgroups in one study (22) and between IGT and NGT in another study (23). In that same study, lower insulin sensitivity is evident in the type 2 diabetes group compared with the normal glucose tolerance group and compared with the prediabetic groups after controlling for overweight (23) consistent with our current and previous findings (12).

Presently, using the hyperglycemic clamp allowed us to examine 2nd phase insulin secretion which is not widely available in the published literature. The defect in first phase insulin secretion in our prediabetes groups is consistent with the findings of Cali et al of decreased glucose sensitivity of 1st phase insulin secretion in the prediabetic state. In their study absolute values of 1st and 2nd phase insulin levels were not significantly different in the prediabetes groups compared with the NGT group, and glucose sensitivity of 2nd phase insulin was not affected except in the combined IFG/IGT group (11). Their study, however, did not include subjects with type 2 diabetes to allow them to evaluate the

magnitude of impairment across the spectrum of glucose tolerance. In our study, inclusion of adolescents with T2DM allowed us to assess not only deviations from normal but also differences from the extreme abnormal. While absolute levels of second phase insulin were significantly lower in T2DM vs. IGT, there was no difference between T2DM and IFG or coexisting IFG/IGT. Such an observation suggests that in IFG the impairment in insulin secretion may play a more critical role in the progression to T2DM than is the case with IGT. Another contrast between the two studies is the study population. While our participants were limited to a balanced representation of AA and Caucasians, their study included subjects of multiple ethnicities with a significant number of Hispanics who may differ in their metabolic response to perturbations in glucose homeostasis. In studies limited to Latino adolescents, investigators did not find significant differences in acute insulin response between IFG and NGT (10) or between IGT and NGT (24), although GDI was reduced in the IFG and IGT groups compared with NGTs indicating an impairment in beta cell function relative to insulin sensitivity.

Several adult studies suggested that the impaired fasting glucose (IFG) state is characterized by hepatic insulin resistance measured during the euglycemic clamp (9,15,25). However, the population in those studies consisted of Mexican American adults in one (15) and Native American (9) in another. Additionally, the prediabetic subjects had higher BMI and waist circumference (15) compared with the NGT group which could have contributed to their hepatic insulin resistance. In a study by Bock et al, mild hepatic insulin resistance was found in IFG Caucasian subjects compared with NGT, and was attributed to increased gluconeogenesis. However, again the IFG subjects were significantly more obese and had higher visceral fat (25). Our study participants in the 5 different groups had comparable degrees of total and abdominal adiposity, and thus it is possible that with similar degrees of obesity, the earliest detected abnormality is in β-cell function and insulin secretion, and hepatic insulin resistance develops later, and be more marked in certain ethnic backgrounds. Therefore, we propose that the defect in insulin secretion in the IFG group in combination with hepatic insulin resistance (which we did not measure during the clamp) may be responsible for the mild fasting hyperglycemia. On the other hand, the interplay between impaired insulin secretion and peripheral insulin resistance in subjects with coexisting IFG/IGT may prevent maintaining plasma glucose within a normal range after a glucose load.

One limitation in our study is the relatively smaller sample size of IFG and combined IFG/IGT groups. However, the use of the clamp, a sensitive method for assessing insulin sensitivity and secretion, allowed us to demonstrate significant differences in 5 group comparison.

In summary, all prediabetic states in obese youth have impaired insulin secretion relative to insulin sensitivity, although the magnitude of impairment in β-cell function may be variable. Such differences potentially translate to a differential in the risk of progression to T2DM. Further investigations into the underlying mechanisms/reasons are needed. The ultimate objective from such scientific advances is to individualize the therapeutic/preventive approach to the specific underlying metabolic dysfunction leading to T2DM at a young age.

Author contributions. FB: Conducted the study, obtained funding, acquired data, analyzed data, and wrote the manuscript. SL: Contributed analytical tools for body composition. NG: Initiated project and acquired data. SA: Study concept and design,

acquisition of data, obtained funding, administrative technical and material support, study supervision and critical revision of the manuscript for intellectual content.

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Table 1: Phenotypic and Metabolic characteristics of obese adolescents with normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), coexistent (IFG/IGT) and type 2 diabetes (T2DM).

	NGT	IFG	IGT	IFG/IGT	T2DM	P-
	(n=24)	(n=13)	(n=29)	(n=11)	(n=30)	value#
Age (years)	13.9±1.9	14.9±1.9	14.5±2.0	14.3±2.1	15.3±1.7	ns
Sex (M/F)*	9M / 15F	7M /6F	6M/23 F	5M / 6F	13M /17F	ns
Ethnicity:*						
AA	10	7	6	6	16	ns
AW	14	6	23	5	14	
Tanner Stage*						
II-III	6	1	5	3	2	ns
IV-V	18	12	24	8	28	
BMI (kg/m^2)	36.2±4.1	33.5±6.9	37.3±7.3	36.0±6.5	36.8±5.3	ns
Waist circumference(cm)	108.2±14.6	100.0±14.9	106.0±14.9	109.3±13.1	108.6±13.6	ns
% Body Fat (%)	46.5±5.5	41.3±7.4	45.5±5.1	44.7±5.3	41.7±6.3	ns
Subcutaneous Abdominal Fat (cm^2)	551.4±138.6	452.1±192.0	563.4±167.4	511.3±147.2	542.1±136.1	ns
Visceral Fat (cm^2)	72.4	67.8	82.0	50.7	78.3	ns
	(46.8-93.4)	(46.8-91.0)	(55.6-104.0)	(40.6-92.6)	(62.4-88.6)	
HbA1c (%)	5.3±0.4[a]	5.6±0.4[b]	5.4±0.4[c]	5.2±0.5[d]	6.6±0.8[a,b,c,d]	<0.001
Fasting glucose (mg/dl)	92.0	102.6	92.15	104.5	118.4	<0.001
	(88.3-96.1)	(100.17-104.75)	(89.0-94.5)	(101.8-108.7)	(103.1-138.5)	
Fasting insulin (µu/ml)	37.4	26.3	39.1	36.8	40.4	ns
	(29.8-44.2)	(21.7-56.6)	(27.4-55.6)	(28.4-56.1)	(33.9-57.2)	
Fasting glucose to insulin ratio	2.5 (2.0-3.3)	3.9 (1.9-4.8)	2.2 (1.7-3.5)	2.8 (2.0-3.8)	3.1 (2.4-4.1)	ns
Proinsulin to insulin ratio	0.17	0.14	0.13	0.18	0.20	0.002
	(0.10-0.2)	(0.12-0.16)	(0.09-0.15)	(0.09-0.25)	(0.09-0.35)	
Postabsorptive hepatic glucose production (mg/kg/min)	1.9	2.1	2.1	2.5	2.4	0.007
	(1.7-2.3)	(2.0-2.7)	(1.7-2.6)	(1.9-2.9)	(2.1-3.2)	
Postabsorptive hepatic insulin resistance (mg/kg/min. µu/ml)	75.1	83.7	83.9	98.2	102.4	0.05
	(53.3-106.6)	(48.3-116.3)	(58.6-130.9)	(60.2-169.7)	(71.4-180.1)	
Cholesterol (mg/dl)	170.1±36.6	157.2±36.9	171.3±35.9	175.1±39.8	158.1±29.4	ns
HDL (mg/dl)	39.1	36.9	38.0	38.1	38.7	ns
	(34.4-49.6)	(30.6-45.3)	(32.4-44.6)	(33.5-45.6)	(33.1-41.8)	
LDL (mg/dl)	104.0±34.4	94.1±30.7	103.3±32.5	110.1±32.0	94.0±27.3	ns
Triglycerides (mg/dl)	110.0	84.0	108.0	109.0	108.0	ns
	(92.0-161.0)	(75.5-157.5)	(92.0-189.0)	(102.5-142.8)	(87.0-148.8)	
TG/HDL ratio	2.8 (1.8-3.8)	2.0 (1.7-5.0)	2.9 (2.1-5.3)	3.0 (2.7-3.8)	3.1 (2.2-4.4)	ns

Data are means ± SD. Cells with 2 values in parentheses indicate median (25^{th} %, 75^{th} %).
#: P-value from ANOVA for continuous variables with means presented, Kruskal-Wallis test with medians presented and chi-square* for categorical variables. Pairs of superscript letters are significant post-Hoc analysis (Bonferroni correction): P<0.05 a: T2DM vs NGT, b: T2DM vs IFG; c: T2DM vs IGT; d: T2DM vs IFG/IGT.

Body composition data was missing in 2 NGT, 2 IGT and 5 T2DM subjects who exceeded the weight limit of 250 lbs of the DEXA machine.

FIGURE LEGENDS:

Figure 1: A) Insulin-stimulated total, oxidative and non oxidative glucose disposal in normal glucose tolerance or NGT (empty bars), impaired fasting glucose or IFG (dotted bars), impaired glucose tolerance or IGT (stripped bar), coexistent IFG and IGT or IFG/IGT (diamond bars) and type 2 diabetes or T2DM (dark bars). P values are for trend (ANOVA p-values). B) 1st and 2nd phase insulin levels during the hyperglycemic clamp in NGT (empty circles), IFG (empty diamond), IGT (empty squares), IFG/IGT (stars) and T2DM (filled squares). C) Glucose disposition index in NGT (empty bars), IFG (dotted bars), IGT (stripped bar), IFG/IGT (diamond bars) and T2DM (dark bars).
In A and C: Pairs of letters are significant post-Hoc analysis (Bonferroni correction): $P<0.05$ a: T2DM vs NGT, b: T2DM vs IFG; c: T2DM vs IGT; e: NGT vs IFG/IGT; f: NGT vs IGT. Data: Mean± SD.

Figure 2: A) Relationship of glucose disposition index to fasting plasma glucose, and B) 2hr OGTT glucose level in normal glucose tolerance (NGT) (empty circles), impaired fasting glucose (IFG) (empty diamond), impaired glucose tolerance (IGT) (empty squares), coexistent IFG and IGT (IFG/IGT) (filled triangles) and type 2 diabetes (T2DM) (filled squares).

Figure 1

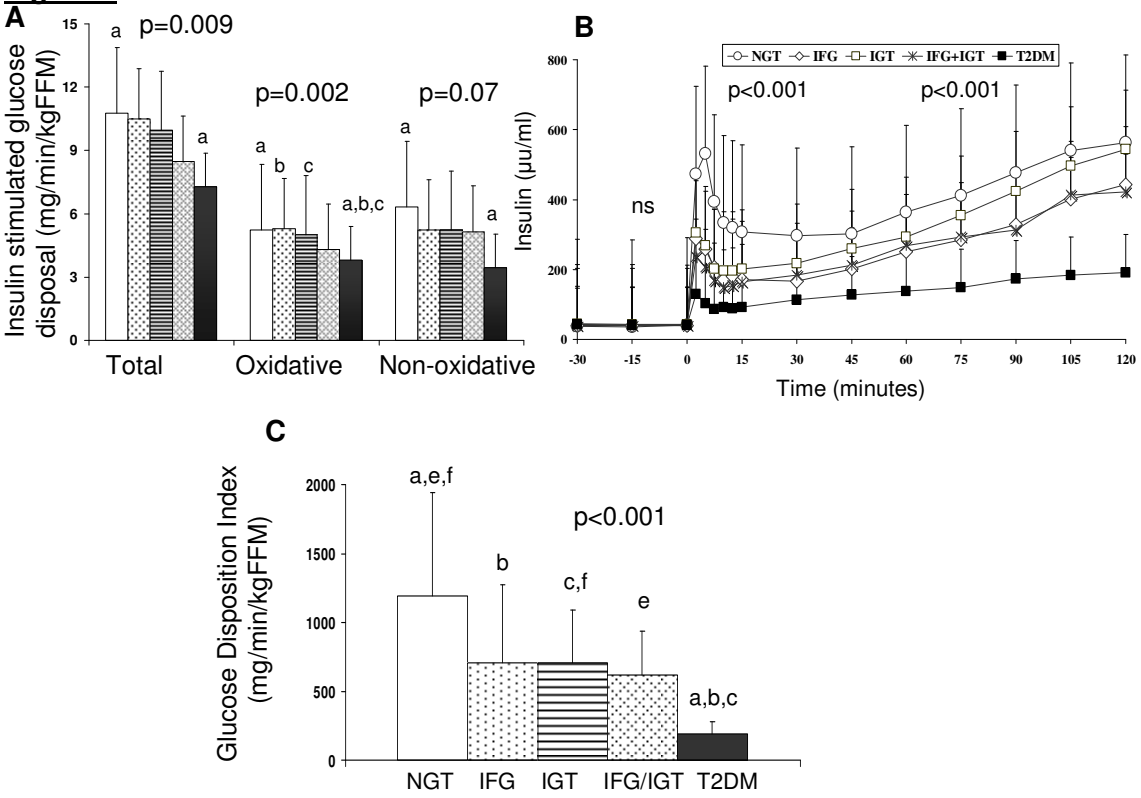

Figure 2