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Potential of abnormalities in myocardial metabolism with the development of diabetes in women with obesity and insulin resistance

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Abstract

Background—Because studies in animal models of type-2 diabetes mellitus (DM) show that excessive myocardial fatty acid (FA) metabolism (at the expense of glucose metabolism) cause cardiac dysfunction, we hypothesized that women with DM would have more FA and less glucose myocardial metabolism than normal or even obese (OB) women.

Research Design and Methods—Women who were lean volunteers (NV) (N = 14; age 35 ± 17 years, body mass index 23 ± 1 kg/m²), OB (N 5 28; 31 ± 6 years, BMI 39 ± 7 kg/m²), and DM (n = 22; 54 ± 11 years, BMI 38 ± 5 kg/m²) were studied. Cardiac positron emission tomography was performed for the determination of myocardial blood flow, oxygen consumption, FA and glucose metabolism. Cardiac work was measured by echocardiography and efficiency by the ratio of work to myocardial oxygen consumption.

Results—Fractional glucose uptake was comparable between NV and OB but lower in DM ($P < .05$ versus NV). Myocardial FA utilization and oxidation were both higher in DM compared with NV and OB ($P < .0001$). Myocardial FA utilization and oxidation had positive correlations with HOMA ($R = 0.35$, $P = .005$ and $R = 0.40$, $P = .001$, respectively) whereas fractional glucose uptake exhibited an inverse correlation ($R = -.31$, $P = .01$). Cardiac work and efficiency were similar among the three groups.

Conclusions—In women, the presence of OB and DM compared with OB alone is associated with a greater reliance on myocardial FA metabolism at the expense of glucose metabolism. These

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Conflict of interest

The authors have indicated that they have no financial conflicts of interest.

perturbations in myocardial metabolism are not associated in a decline left ventricular efficiency or function suggesting that the metabolic perturbations may precede an eventual decline left ventricular function as is seen in animal models of DM.

Keywords

Fatty acid imaging; glucose; metabolism: PET; diabetes

INTRODUCTION

Over the past several decades the prevalence of obesity has increased significantly in the United States and worldwide.¹ Because obesity and its complication of insulin resistance is a precursor for type-2 diabetes mellitus, the prevalence of diabetes mellitus has risen at a similarly alarming rate.^{1,2} Both obesity and type-2 diabetes mellitus are predictors of left ventricular dysfunction and heart failure, independent of other associated co-morbidities such as coronary artery disease and hypertension.^{3,4} However, once heart failure occurs the presence of obesity is associated with a survival benefit, the so called obesity paradox.⁵ In contrast, the prognosis in heart failure patients with type-2 diabetes mellitus is significantly poorer than in patients with heart failure alone. Moreover, women with type-2 diabetes mellitus are several times more likely to develop heart failure and have an even worse prognosis than men with diabetes.^{6,7}

Perturbations in myocardial substrate metabolism have been described in both obesity and type-2 diabetes mellitus and may play a central role in the cardiac manifestations observed clinically.⁸⁻¹⁰ Excessive dependence by the heart on fatty acid (FA) metabolism to meet its energy needs characterizes the metabolic phenotype in experimental models of both conditions.^{11,12} An increase in FA delivery to the heart, either bound to albumin or incorporated into triglycerides, due to the effects of insulin resistance on peripheral tissues, appears to be a major contributor to the over-dependence on FA metabolism.^{8,10} This metabolic perturbation causes ventricular systolic and diastolic dysfunction in animal models of diabetes mellitus by impairing the energetic profile, reducing anaplerosis, and increasing free radical formation and apoptosis (so-called lipotoxicity).^{8,12}

We have shown previously that in obese women, both myocardial FA uptake and oxidation are increased and directly correlate with the degree of insulin resistance, but no changes in myocardial glucose uptake were observed.¹³ Results of studies in experimental models of combined obesity and diabetes mellitus have demonstrated that progressive insulin resistance and worsening myocardial FA metabolism precede the reduction in myocardial glucose uptake that occurs with development of diabetes mellitus, which presages the development of cardiac dysfunction.^{11,12} The goal of this study was to determine if this progression in the pattern of myocardial substrate metabolism due to obesity and diabetes mellitus was present in humans. We hypothesized that myocardial FA metabolism would be higher and glucose metabolism lower in women with both obesity and type-2 diabetes mellitus compared with women with obesity alone. To this end measurements of myocardial substrate metabolism and left ventricular stroke work were measured in three groups of women, normal lean volunteers (NV), obese OB, and those with both obesity and type-2 diabetes mellitus (DM).

METHODS

Study Population

We studied 64 women: 14 NV, 28 OB, and 22 DM (Table 1). Data from a portion of the NV and OB subjects were reported previously in a study comparing the metabolic changes

between lean and obese women.¹³ Entry criteria included a body-mass index (BMI) ± 25 kg/m² for NV, ≥ 30 kg/m² for both the OB and the DM groups. Only women were studied to reduce the confounding effects of gender on the myocardial metabolic phenotype.^{14,15} All subjects completed a comprehensive medical evaluation that included a history, physical examination, routine blood tests, and a fasting lipid profile. Normal volunteers and OB subjects were normotensive and underwent a 2-hour glucose tolerance test to exclude diabetes mellitus. Subjects with DM were treated with metformin with or without a sulfonylurea, were required to be naive to exogenous insulin, have well-controlled indices of glycemia (hemoglobin A1c < 7%), be non-smokers, have controlled blood pressure with or without therapy (defined as a systolic blood pressure < 140 mm Hg and a diastolic pressure < 90 mm Hg), and have normal total cholesterol (<220 mg/dL) and low-density lipoprotein cholesterol (< 130 mg/dL) levels with or without treatment with an HMG-CoA reductase inhibitor. For all subjects subclinical coronary artery disease and other forms of cardiac disease were excluded with a normal electrocardiogram and rest/stress echocardiogram. Subjects with persistent hypertension despite therapy, a history of coronary artery or other cardiac disease, a history of smoking cigarettes within the last 12 months, or who were pregnant or lactating were excluded. The Institutional Review Board at the Washington University School of Medicine approved this study. All subjects provided written informed consent before enrollment.

Imaging Protocol and Analysis

Subjects were admitted to the Inpatient Research Unit of Washington University School of Medicine the evening before the positron emission tomography (PET) study. At 6 pm the night before, all subjects ingested a standard meal containing 12 kcal/kg body weight for NV and 12 kcal/kg adjusted body weight for the OB and DM groups (adjusted body weight = ideal body weight + [(actual body weight – ideal body weight) $\times$ (0.25)]). Ideal body weight was determined by the midpoint the medium frame of the Metropolitan Life Insurance Company Tables.¹⁶ Most of the increase in body weight in OB represents an increase in fat mass. Adipose tissue has lower energy requirements than lean tissue. Therefore, providing the same calories *per kg body weight* in NV and OB would deliver an excessive amount of calories in relationship to energy requirements in obese than in lean subjects. The formula used for adjusting energy intake in the obese group is an empiric formula that has been used by other investigators for many years in an effort to normalize calorie intake with calorie requirements.^{17,18} The following morning, after subjects fasted overnight (12 hours), two 18- or 20-gauge catheters were inserted into antecubital veins for radiopharmaceutical injections and blood sampling.

All studies were performed on a commercially available tomograph (Siemens ECAT 961 HR and ECAT 962 HR+, Siemens Medical Systems, Knoxville, Tennessee). Studies were performed under resting conditions starting at 8 am and ending at approximately 1:30 pm to avoid circadian variations in myocardial metabolism.¹⁹ Measurements of myocardial blood flow (MBF), myocardial oxygen consumption (MVO₂), and myocardial glucose and FA metabolism were obtained with PET using ¹⁵O-water, 1-¹¹C-acetate, 1-¹¹C-glucose, and 1-¹¹C-palmitate, respectively. The effective dose for a complete PET study was 13 mSv. In conjunction with well-validated compartmental modeling schemes, measurements of MBF, (mL/g/min), MVO₂ (μ mol/g/min), fractional glucose uptake (mL/g/min) and overall utilization (nmol/g/min), and fractional FA uptake (mL/g/min), overall utilization and oxidation (nmol/g/min) were performed as previously reported.^{13,20} In brief, both fractional glucose and FA uptake are calculated by the product of the extraction fraction for each substrate (derived from their respective mathematical models) and blood flow and thus represent the fraction of these substrates taken up by the heart independent of plasma substrate levels.¹³ In contrast, myocardial glucose and FA utilization were obtained by

multiplying substrate uptake by their corresponding concentrations in the blood and reflect the total uptake of substrate and its subsequent metabolism. Myocardial FA oxidation represents the amount of extracted FA that is oxidized per gram of LV myocardium.

Measurements of Plasma Insulin, Substrates, Radiolabeled Metabolites, Whole Body Insulin Resistance and Body Composition

Blood samples were obtained at predetermined intervals during the study to measure plasma substrates (glucose, FAs, and lactate) and insulin levels. Glucose and lactate levels were measured using a commercially available glucose-lactate analyzer (YSI, Yellow Springs, Ohio). Plasma-free FA levels were determined an enzymatic method (NEFA C kit, Wako Chemicals USA, Richmond, VA). Plasma insulin levels were measured by radioimmunoassay (Linco Research Inc., St Charles, Missouri). In addition, plasma levels of $^{11}\text{CO}_2$ values and ^{11}C -lactate were measured to correct for the arterial input function during compartmental modeling of the myocardial kinetics of the various metabolic tracers. Insulin resistance was calculated using the homeostasis model assessment (HOMA) = (fasting insulin [$\mu\text{U/mL}$] $\times$ fasting glucose [mM/L] divided by 22.5). Total body fat and fat-free mass was determined by dualenergy x-ray absorptiometry (DEXA, Hologic QDR 2000/w, Waltham, MA).

Echocardiography

Immediately following PET imaging, subjects underwent echocardiography. Ejection fraction was calculated using the modified Simpson method. From the echocardiograms left ventricular mass was determined using the area-length method, and left ventricular mass index = left ventricular mass/body surface area according to the recommendations of American Society of Echocardiography.²¹ Cardiac output was calculated as the time-velocity integral of the left ventricular outflow $\times$ outflow tract area and cardiac work as output $\times$ mean arterial pressure. Cardiac work and oxygen consumption were converted j/g/min as previously described.¹⁴ Efficiency was the ratio of work/oxygen consumption.¹⁴

Statistical analysis

All results are expressed as mean $\pm$ SD. Between group differences were evaluated using analysis of variance with analysis of covariance being used to adjust for covariates that might explain group differences in outcome measures. Pearson correlation coefficients were used to evaluate the association between continuous parameters. *P* values less than .05 were considered statistically significant.

RESULTS

Baseline characteristics are presented in Table 1. The DM subjects were older than the other two groups. As a consequence there were a significantly higher proportion of diabetic women that were post-menopausal compared with the other two groups. Importantly, there was no difference in BMI between the OB and DM groups. Despite good glycemic control, the DM group had a worse whole body metabolic profile than the NV and even the OB group, with higher plasma triglyceride, FA, glucose, and insulin levels and higher insulin resistance, as calculated by HOMA. The duration of DM was relatively short, and as aforementioned, no subject required exogenous insulin therapy.

Hemodynamics, MBF and MVO_2 , Left Ventricular Structure and Function

Shown in Table 2 are the measurements for hemodynamics, MBF, MVO_2 , left ventricular mass and function. No differences between the groups were noted with respect to heart rate; however, systolic blood pressure increased from NV to OB and from OB to DM. MBF and

MVO₂ were highest in the OB group. Both the left ventricular mass index and ejection fraction were within the normal range and similar among the three groups ($P = \text{NS}$). Cardiac work was higher in the OB and DM groups compared with the NV group, paralleling the increased MVO₂ in the former. As a consequence, myocardial efficiency was similar among the three groups.

Myocardial Glucose Metabolism

Shown in Figure 1 are values for fractional myocardial glucose uptake and glucose utilization. Fractional uptake (in mL/g/min) was lower in the DM group compared with the NV (0.024 ± 0.013 vs. 0.039 ± 0.032 , respectively, $P < .05$) but not different than the OB (0.034 ± 0.026). Similarly, glucose utilization (in nmol/g/min) trended toward being the lowest in the DM (130 ± 66); however, the differences between the DM and the NV (202 ± 182) and OB (149 ± 116) were not significant, likely reflecting the contribution of increased plasma glucose in the DM group to the calculation of their glucose utilization. An additional comparison of glucose utilization per μU of plasma insulin at the time of the PET suggests that the myocardium of the DM (15 ± 14 [nmol/g/min]/ μU) and the OB (25 ± 35 [nmol/g/min]/ μU) are more insulin resistant than that of the NV (and 46 ± 38 ; $P < .01$ and $P < .05$, respectively). Values in the DM group tended to be lower than the OB group but did not reach statistical significance ($P = .1$).

Myocardial FA Metabolism

Shown in Figure 2 are the mean values for plasma FA levels, fractional FA uptake, FA utilization, and oxidation. Plasma FA levels (nmol/mL) were highest in DM (1026 ± 326) compared with either OB (640 ± 173) and NV (572 ± 187), $P < .0001$. There were no differences across the groups in fractional FA uptake. However, myocardial FA utilization and oxidation (both in nmol/g/min) were higher in DM (226 ± 82 and 186 ± 82) compared to NV (123 ± 38 and 108 ± 28) and OB (149 ± 51 and 135 ± 46), $P < .001$. Of note, values for %FA oxidation, a measure of the fraction of extracted 1-¹¹C-palmitate that was oxidized were marginally lower in the DM subjects (83 ± 1) compared to NV (89 ± 12) and OB (91 ± 11) but the differences were not significant.

Age Correction of the Metabolic Variables

Given the older age of the DM group all of the analyses were repeated after adjusting for both age and group. Again we observed significant differences among the groups with respect to HOMA ($P < .0001$), glucose utilization per μU of plasma insulin ($P < .03$), plasma FA levels ($P < .004$), FA utilization ($P < .005$) and FA oxidation ($P < .04$). Only the difference in the fractional glucose uptake lost significance ($P = .12$) with this analysis.

Correlation of Myocardial Fuel Utilization with HOMA

The univariate correlation of various metabolic measurements and HOMA is shown in Table 3. As expected, plasma FA levels were positively correlated with HOMA. Fractional glucose uptake was negatively correlated with HOMA, suggesting that increasing peripheral insulin resistance had a detrimental effect on the fractional uptake of glucose by the heart. The correlation of HOMA with overall myocardial glucose utilization was similar but weaker, again likely reflecting the confounding effects of the slightly higher plasma glucose levels in the DM subjects. Conversely, myocardial FA utilization and oxidation were positively correlated with HOMA across all women studied. These results suggest that as peripheral insulin resistance increases, overall myocardial glucose utilization declines and myocardial FA utilization and oxidation increases. However, when adjusted for age and group HOMA was not a significant predictor for any of the significant variables from Table 3.

DISCUSSION

To our knowledge, this is the first study to show that the hearts of women with both OB and DM utilize excessive amounts of FA, even when compared to those of OB (nondiabetic) women, and this excessive FA use in DM is at the expense of glucose use—a change not seen in OB women. Moreover, these metabolic changes appear to precede changes left ventricular work and efficiency. Since the myocardial fractional uptake of FA was not different across groups, the increase in myocardial FA metabolism appears to be due to an increase in plasma FA delivery. In addition, while the differences between groups in fractional myocardial glucose uptake and utilization were of borderline significance, they become much more pronounced when referenced to the plasma insulin environment, suggesting that the myocardium can show measurable insulin resistance. The significance of these observations is twofold: (1) They provide first confirmation that the metabolic changes observed in experimental models of OB and DM are present in humans with the disease, which further suggests that the metabolic mechanisms that cause diabetic heart failure in animals are likely germane to human disease and; (2) These findings suggest that the metabolic alterations precede a decline in LV systolic function and may indicate a role for metabolic manipulation to prevent and treat diabetic cardiomyopathy. This has significant potential clinical impact given the dramatic increase in incidence and prevalence of obesity and diabetes and the consequent increase expected in diabetic cardiomyopathy.

Comparison with Prior Studies

The findings from this study are consistent with those observed in genetic models of OB and DM which demonstrate a similar temporal pattern of elevation in myocardial FA uptake and oxidation preceding abnormalities in myocardial glucose use.^{12,22} As we have shown previously, OB women also demonstrate increased myocardial FA metabolism but not impaired glucose uptake.¹³ It is well documented that in DM there is a decrease in myocardial glucose uptake under conditions of euglycemia and physiological insulin levels.^{23–25} In this study, the average fractional glucose uptake was also lower in the DM, compared with the NV (similar to previous studies), but myocardial glucose utilization was not lower. Several factors may have contributed to this finding. First, in previous studies, patients with DM were typically studied during insulin supplementation and/or glucose loading to accentuate the myocardial glucose use differences. In this study, metabolic measurements were performed under fasting conditions to enhance changes in myocardial FA metabolism. Under these conditions, normal myocardial glucose use is low making it more difficult to distinguish a difference between normal, low glucose metabolism and lower metabolism in DM. Second, the DM patients were ~ 20 years older than either the NV or OB groups. We have shown previously that with moderate aging myocardial glucose uptake increases.²⁰ Thus, aging may have increased glucose use in the DM relative to the other two groups. Finally, although the DM group exhibited excellent glycemic control per their HbA1c, their plasma glucose levels at the time of the PET were higher than in the other groups, which necessarily increased their myocardial glucose utilization.

Heretofore, the measured level of myocardial FA metabolism in patients with DM has been quite variable ranging from reduced to normal to increased when compared with non-diabetics.^{26–29} The variability in FA metabolism is in contrast to studies in experimental models of DM where an increase in myocardial FA metabolism is a consistent finding. In general, the variability in humans appears to be related to the methods used to measure FA metabolism (e.g., semi-quantitative techniques using tracer analogues), the patient population (e.g., patients with and without coronary artery disease) studied and the plasma insulin and substrate environment at the time of the study (e.g., fasting versus insulin clamp). Recently in non-obese males with DM, it was shown that myocardial FA metabolism was increased compared with non-obese controls.³⁰ The results of this study

confirm these observations and extend them to women with DM and in the setting of concurrent obesity. Taken in sum, the results of these two studies appear to help resolve some of the discrepancies from prior studies. That is, in otherwise healthy patients with DM studied under resting fasted conditions, using quantitative imaging methods of a radiotracer that faithfully tracks unlabeled palmitate, myocardial FA metabolism is increased when compared with non-diabetics.

We observed that cardiac work was increased in both OB and DM subjects compared with NV subjects but was matched by an increase in MVO_2 resulting in similar left ventricular efficiency values across all three groups (Table 2). These findings differ from what has been in experimental models of OB and DM where efficiency is typically reduced.^{31,32} However, in the animal models the DM is untreated and poorly controlled as opposed to our human subjects. In a similar vein, our current results differ from those of our earlier study in NV and OB women which observed similar levels of cardiac work but reduced efficiency in the OB subjects.¹³ Differences in the loading conditions of the individuals in the two studies may explain some of the difference in results since the systolic blood pressure was lower in the NV and higher in the OB in this study compared with the previous study.

Potential Mechanisms for the Metabolic Differences

The results of this study confirm the prominent role of peripheral insulin resistance and its effects on myocardial plasma FA delivery in defining the myocardial metabolic phenotype in NV, OB alone, and DM with obesity (Figure 2; Table 3). The increase in plasma FA levels likely reflects the combined effects of progressive reduction in insulin action on adipocytes superimposed upon an increased fat mass (Table 1). Moreover, because the fractional uptake of FAs was similar in all three groups (Figure 2) the increase myocardial FA uptake and oxidation is likely attributable to primarily an increase in FA delivery.

Myocardial glucose uptake per level of insulin progressively declined from NV to OB to DM groups supporting a role for myocardial insulin resistance in defining the metabolic phenotype during this transition. Much of this effect may be explained by the Randle Cycle with the increase in myocardial FA oxidation leading to an inhibition of various steps of glycolysis; most prominently at the level of pyruvate dehydrogenase and to lesser extent 6-phosphosphofructo-1-kinase. The subsequent increase in glucose-6-phosphate concentration inhibits hexokinase which then inhibits glucose uptake.³³ Other mechanisms are also likely operational. For example, basal glucose uptake in isolated cardiomyocytes is significantly reduced in hearts from mice with cardiomyocyte-restricted deletion of the insulin receptor suggesting insulin does mediate GLUT-1 transporter function.³⁴ Moreover, studies in skeletal muscle of normal humans have also demonstrated that accumulation of intramyocellular lipid (a likely consequence of increased FA metabolism) during Intralipid infusion directly correlates with insulin resistance.³⁵ A similar relationship has been observed in OB and DM.³⁶ Although not fully elucidated, other potential mechanisms include activation of various isoforms of protein kinase C, which are capable of phosphorylation of the insulin receptor and/or the insulin receptor substrates and inhibition of insulin signaling at the level of protein kinase B, possibly via ceramide-dependent pathways.^{37–39} Finally, the potential role of inflammation increasing myocardial insulin resistance cannot be excluded, given the general increase in inflammatory markers in OB and DM.⁴⁰

Study Limitations

A limitation in this study was that it was performed on a cross-sectional cohort rather than a longitudinal assessment of the transition between disease entities. The ideal study to delineate the transition in metabolism and function is a longitudinal study in subjects as they

move from one group designation to another. While such a study is routinely performed in animals, it is likely impossible to perform in humans given the inability to predict when patients will transition from one group to another and the cost involved in performing the necessary serial studies. Although the DM group was older than the other groups, we believe our observations were not attributable to an age effect. For example, after age-adjustment the same patterns in myocardial substrate use between the groups were present as was seen without age-adjustment. Also, we have reported that with age myocardial FA use declines and glucose metabolism increases, so if anything the age difference actually masked further increases in FA metabolism and a decline in glucose use.²⁰ We chose to only study women given the sexual dimorphism in the myocardial metabolic phenotype in both lean and OB individuals might confound interpretation of the metabolic patterns in the DM group compared with the OB group. Clearly, future studies are needed to see if similar metabolic changes occur in obese men. Although by univariate analysis, we observed a correlation between insulin resistance (as measured by HOMA) and the measurements of myocardial FA and glucose metabolism, this relationship was lost after adjusting for age and group. The lack of correlation was likely attributable to inadequate power to evaluate these relationships. The PET approach used for quantifying myocardial FA metabolism does not account for the contribution of plasma triglycerides or endogenous triglycerides to FA myocardial FA metabolism. In experimental models of DM there is an increase in myocardial oxidation rates of extracted FAs, derived from plasma chylomicrons via lipoprotein lipase.⁴¹ Therefore, myocardial FA utilization and oxidation in DM may be *even greater* than the significant differences we have shown in this study. Finally, it is becoming increasingly apparent that OB and DM are heritable traits that reflect the complex interaction between genetic and environmental factors.⁴² Unfortunately, this study was not adequately powered to address this interaction.

Potential Clinical Implications

Overdependence on FA metabolism by the heart has many clinical implications. For example, the heart needs to be able to switch substrate use depending on substrate availability and physiologic or pathophysiologic conditions. If the diabetic heart is less well-equipped to switch to glucose use this may be detrimental to its adaptability and survival in conditions that require glucose use (e.g., ischemia). Further studies in diabetic patients with ischemia are necessary to test this theory. Moreover, the presence of increased FA oxidation may lead to an overproduction of reactive oxygen species and their attendant pathological effects on ion channels, calcium homeostasis, mitochondrial function, and cell survival. Furthermore, excessive myocardial FA uptake may lead to the accumulation of lipid intermediates, which can further impair cell survival and left ventricular function, in a process known as lipotoxicity.

Framingham data have previously shown that heart failure is $5 \times$ more common in diabetic women than those without diabetes but only $2 \times$ as common in diabetic men.⁶ Although requiring further study, the excessive myocardial FA and impaired glucose metabolism we have shown in women with DM may have detrimental effects on myocardial tissue and thus may provide a partial explanation for the remarkably high heart failure rates and consequent mortality seen in women with DM.

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Figure 1.

Measurements of plasma glucose levels during the positron emission tomography (PET) study, fractional glucose uptake, glucose utilization, and glucose utilization per plasma insulin level in lean volunteers (NV), obese (OB) and obese/diabetic women (DM). [#] $P < .0001$ vs NV, ^{*} $P < .05$ vs NV, ^{**} $P < 0.01$ vs NV.

Figure 2.

Measurements of plasma-free fatty acid (FA) levels during the positron emission tomography (PET) study, fractional FA uptake, overall utilization, and oxidation in lean volunteers (NV), obese (OB) and obese/diabetic women (DM). * $P < .0001$ vs NV and OB.

Table 1

Baseline characteristics

	NV	OB	DM	ANOVA <i>P</i> values
Number of volunteers	14	28	22	
Age (years)	35 ± 17	31 ± 6	54 ± 11 [*]	<.0001
Post-menopausal (N)	4	1	15	<.0001
Body Mass Index (kg/m ²)	23 ± 1	39 ± 7 [#]	38 ± 5 [#]	<.0001
Percent fat mass (%)	31 ± 6	49 ± 14 [#]	45 ± 3 [#]	<.0001
Total serum cholesterol (mg/dL)	170 ± 369	176 ± 40	167 ± 29	NS
Serum triglycerides (mg/dL)	84 ± 24	95 ± 54	134 ± 44 ^{**}	<.005
Low-density lipoprotein (mg/dL)	94 ± 34	106 ± 32	96 ± 35	NS
High-density lipoprotein (mg/dL)	59 ± 18	50 ± 13	49 ± 7	NS (0.1)
Plasma fatty acid (μmol/mL)	572 ± 187	643 ± 176	1011 ± 326 [*]	<.0001
Plasma glucose (μmol/mL)	5.0 ± 0.4	4.7 ± 0.4	6.6 ± 1.8 [*]	<.0001
Plasma insulin (μU/mL)	5.5 ± 2.7	9.2 ± 4.8	15.1 ± 10.6 [*]	<.001
HOMA (μU/L · mmol/L)	1.30 ± 0.68	1.95 ± 1.11	4.31 ± 2.92 [*]	<.0001
Hemoglobin A _{1c} (%)			6.5 ± 0.6	
Duration of diabetes (years)			6.4 ± 0.4.5	

NV, OB, and DM: lean, obese, and type 2 diabetic volunteers, respectively;

^{*} *P* < .0001 vs NV,

[#] *P* < .01 vs NV.

^{**} *P* < .005 vs NV, OB

Table 2Hemodynamics, MBF, MVO₂, and left ventricular structure and function

	NV	OB	DM	ANOVA <i>P</i> values
Heart rate (bpm)	66 ± 12	67 ± 11	70 ± 11	NS
Systolic blood pressure (mm Hg)	105 ± 9	118 ± 13 [*]	132 ± 16 ^{**}	<.0001
Rate pressure product (bpm · mm Hg)	7014 ± 1506	7877 ± 1515	9327 ± 1793 ^{**}	<.005
Myocardial blood flow (mL/g/min)	0.98 ± 0.11	1.27 ± 0.39 [*]	1.18 ± 0.26	<.05
MVO ₂ (μmol/g/min)	5.18 ± 0.94	6.49 ± 1.68 [*]	6.18 ± 1.29	<.05
Left ventricular Mass Index (g/m ²)	80 ± 5	79 ± 12	81 ± 14	NS
Left ventricular ejection fraction (%)	65 ± 4	63 ± 6	62 ± 7	NS
Cardiac work (mm Hg · [L/min])	315 ± 18	435 ± 19 [#]	424 ± 31 [#]	<.003
Left ventricular efficiency	13.2 ± 0.8	12.9 ± 0.9	13.7 ± 0.7	NS

NV, OB, and DM: lean, obese, and type 2 diabetic volunteers, respectively;

^{*} *P* < .05 vs NV.^{**} *P* < .005 vs NV, OB,[#] *P* < .02 vs NV

Table 3

Correlations between HOMA and metabolic parameters

Dependent variables	<i>R</i>	<i>P</i> value
Plasma FA level (nmol/mL)	0.35	.005
Fractional myocardial glucose uptake (mL/g/min)	-0.31	.01
Myocardial glucose utilization (nmol/g/min)	-0.21	0.1
Myocardial FA oxidation (mL/g/min)	-0.03	NS
Fractional myocardial FA Uptake (mL/g/min)	0.05	NS
Myocardial FA utilization (nmol/g/min)	0.35	.005
Myocardial FA oxidation (nmol/g/min)	0.40	.001
Myocardial %FA oxidation	-0.13	NS

R Correlation coefficient. *Bolded* data (significant)