Insulin Sensitivity in Women at Risk of Coronary Heart Disease and the Effect of a Low Glycemic Diet

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The risk of coronary heart disease (CHD) is influenced by family history, insulin sensitivity (IS), and diet. Adiposity affects CHD and IS. The cellular mechanism of IS is thought to involve the adipocyte cytokine tumor necrosis factor-alpha (TNF-α). Insulin-stimulated glucose uptake in isolated subcutaneous and omental adipocytes obtained during elective surgery was measured in 61 premenopausal women, 24 with a parental history (PH) of CHD. In vivo IS was measured using the short insulin tolerance test (SITT) in 28 women, 16 with PH-CHD, before and 3 weeks after randomization to a low glycemic index (LGI) or high glycemic index (HGI) diet. In vitro adipocyte IS and TNF-α production was measured following dietary modification. On the habitual diet, in vitro insulin-stimulated glucose uptake in adipocytes as a percentage increase over basal was less in women with PH-CHD than in those without it (presented as the median with 95% confidence limits: subcutaneous, 28% (17% to 39%) *v* 96% (70% to 120%), $P < .01$); omental, 40% (28% to 52%) *v* 113% (83% to 143%), $P < .01$). In vivo IS in 16 PH-CHD subjects and 12 controls before dietary randomization was similar, and increased in both groups consuming a LGI versus HGI diet (PH-CHD, 0.31 (0.26 to 0.37) *v* 0.14 (0.10 to 0.24) mmol/L/min, $P < .01$; controls, 0.31 (0.1 to 0.53) *v* 0.15 (0.06 to 0.23) mmol/L/min, $P < .05$). Adipocyte IS was greater in PH-CHD women on a LGI versus HGI diet (subcutaneous, 50% (20% to 98%) *v* 13% (1% to 29%); omental, 97% (47% to 184%) *v* 29% (4% to 84%), $P < .05$). Adipocyte TNF-α production was higher in women with versus without PH-CHD (subcutaneous, 0.3 (0.18 to 0.42) *v* 0.93 (0.39 to 1.30) ng/mL/min; visceral, 0.22 (0.15 to 1.30) *v* 0.64 (0.24 to 1.1) ng/mL/min, $P < .04$, respectively), but was uninfluenced by the dietary glycemic index. We conclude that in vitro adipocyte IS is reduced and adipocyte TNF-α production is increased in premenopausal women with PH-CHD. A LGI diet improves both adipocyte IS in women with PH-CHD and in vivo IS in women with and without PH-CHD.

CORONARY HEART DISEASE (CHD) is the leading cause of death worldwide.[1] Its prevalence is determined by genetic, metabolic, and life-style factors, including diet. The relative risk of CHD more than doubles when there is a parental history of premature CHD (PH-CHD).[2] Reduced insulin sensitivity (IS) contributes to the metabolic environment that predisposes to CHD.[3] IS itself is influenced by genetic and dietary factors. There is evidence of reduced IS at diagnosis in 60% of patients with CHD.[4] Reduced IS is also found in adolescent children with PH-CHD, a finding that implicates IS in the early pathogenesis of heart disease.[5] In addition, children of parents with diabetes and hypertension, two other conditions associated with premature CHD, have also been reported to show reduced IS.[6,7]

Circulating free fatty acid (FFA) has an influence on IS in muscle and adipose tissue. The sensitivity of adipose tissue to insulin is thought to be a major determinant of whole-body IS.[8] FFA release from adipose tissue into the circulation is under the control of hormone-sensitive lipase, an exquisitely insulin-sensitive enzyme. Adipocytes from individuals with CHD, obesity, and diabetes demonstrate in vitro resistance to insulin.[8-10] The adipocyte cytokine tumor necrosis factor-alpha (TNF-α) is thought to be a modulator of cellular IS by inhibiting key phosphorylation sites in the insulin signaling pathways. Elevated circulating and tissue TNF-α levels have been observed in a variety of insulin-resistant states.[11]

Abdominal obesity is associated with an increased risk of CHD. Metabolic changes occur with increasing visceral obesity, include fasting hyperinsulinemia and decreased plasma high-density lipoprotein (HDL)-cholesterol. These metabolic atherogenic changes associated with abdominal obesity are believed to result from increased FFA reaching the liver as a consequence of reduced visceral adipocyte IS.[12,13] The net effect of increased portal FFA is to decrease glucose oxidation and hepatic insulin clearance while increasing hepatic glucose production and very–low-density lipoprotein synthesis.[14]

An association between CHD and dietary fat intake is well documented; however, the role of dietary carbohydrate in CHD is not. The glycemic index of a carbohydrate is an assessment of its postprandial effect on blood glucose,[15] independent of its chemical composition, chain length, and insoluble fiber content.[16] The lower the glycemic index, the smaller the effect of the carbohydrate on postprandial glucose and insulin values.[16] An original criticism of the use of the glycemic index was the concern that the glycemic index of a mixed meal differed from that of the sum of the constituent parts. However, Wolever[16] has shown that this theoretical concern is not substantiated and the addition of low glycemic index (LGI) carbohydrates to a meal effectively reduces the overall glycemic index of the meal in relation to their percentage contribution to the total carbohydrate content of the meal. Recently, LGI diets have been shown to have a short-term beneficial effect on whole-body IS in subjects with diabetes, CHD, and obesity.[8,17,18] Similar diets have been reported to improve in vitro adipocyte IS.[8] Epidemiological studies undertaken in premenopausal women have shown a beneficial long-term effect of LGI diets to decrease fasting insulin values and reduce the risk of non–insulin-dependent diabetes mellitus (NIDDM).[19] Similar findings have been recently reported in men.[20] The San Luis Valley Diabetes

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Study showed that a habitual diet high in fat and low in starch and fiber (suggestive of a high glycemic index [HGI] diet) was associated with hyperinsulinemia.[21] From these studies, it would appear that a LGI diet would be beneficial in reducing CHD risk factors.

The present study examines whether premenopausal women at risk of CHD have reduced whole-body and in vitro IS and whether the glycemic index of the diet can favorably improve either whole-body or adipocyte IS or influence adipocyte TNF-α production.

SUBJECTS AND METHODS

The Research Ethical Committee of Hammersmith Hospital National Health Service Trust approved the studies.

Subjects

Sixty-one premenopausal women awaiting tubal surgery without a personal or family history of diabetes, hypertension, or other chronic diseases were recruited. Women were grouped according to the presence or absence (controls) of a parental history of CHD (PH-CHD) diagnosed before the age of 55 years. Only healthy women able to provide medical information on their parents' present or past cardiac history were studied. Of 61 women recruited, 33 gave consent for fasting blood samples and fat biopsies to be taken and were willing to record their habitual diet. However, these women did not consent to a short insulin tolerance test (SITT) or to randomization to the dietary intervention of the study. We believe the data collected from this group were too valuable to be excluded; hence, these women form the habitual diet group and were included as part of the larger study.

Diet

All 61 women completed a 7-day diet diary at entry into the study. Energy expenditure was calculated using the Schofield formula[22] and was used to validate the accuracy of the diet diaries. As already stated, the habitual diet group consisted of 33 women unwilling to participate in the dietary intervention or to undergo a SITT. This group consisted of eight women with PH-CHD and 25 controls. The remaining 28 women, 16 with PH-CHD, were randomized to a HGI or LGI diet for a minimum of 3 weeks before surgery. The aim of the dietary intervention was to change only the glycemic index of the diet without affecting other macronutrients. Using methodology previously described,[8] isocaloric diets were individually prescribed to the women using commonly available foods that varied only in the rate of absorption of carbohydrates. Care was taken to ensure that all other macronutrients remained constant. For the LGI diet, rapidly absorbed carbohydrates (foods with a glycemic index > 85) were exchanged for foods that are slowly absorbed and have a LGI (foods with a glycemic index < 85). Examples of LGI foods include pasta, oats, whole grain products, pulse vegetables such as beans and lentils, and whole fruit. Foods that are rapidly absorbed such as sucrose and lactose but have a LGI due to their chemical composition were not included in the LGI diet. The HGI diet consisted of avoidance of foods taken in the LGI diet. Individual compliance to the recommended changes in the glycemic index of the diet while maintaining other macronutrients constant was assessed using 7-day diet diaries completed during the first week of the study. If the glycemic index of the diet was greater than 85 on the LGI diet or less than 85 on the HGI diet, or changes had occurred with the other dietary macronutrients, the subject was reinstructed about the diet and asked to repeat the diet diary over the following week. All subjects completed a diet diary during the last week of the study. From these diet diaries, each individual's glycemic index and compliance were calculated using previously validated techniques and glycemic index tables.[16,23]

Anthropometric and Fasting Biochemical Data

The body mass index (BMI) and waist to hip ratio were calculated for all women on the day before surgery when fasting blood samples for glucose, insulin, total cholesterol, and triglycerides were taken (Table 1). The 28 women randomized to a HGI or LGI diet had similar measurements taken before dietary intervention. Plasma glucose, cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were analyzed by standard colorimeteric techniques (Boehringer Mannheim, Lewes, UK) and plasma insulin by radioimmunoassay as previously described.[24]

In Vitro IS

Adipocyte IS was assessed on dual adipose biopsies taken at the time of surgery in all 61 women. Biopsies (1 to 5 g) were obtained using a scalpel without cauterization; subcutaneous fat was taken from the midpoint of the laparotomy incision, and the visceral sample was from

Table 1. Demographic, Anthropometric, and Fasting Biochemistry Data for Women With PH-CHD and Controls Following Either the Habitual Diet or a 3-Week Diet With a HGI or LGI

	Habitual Diet		HGI Diet		LGI Diet	
Parameter	PH-CHD	Control	PH-CHD	Control	PH-CHD	Control
No. of subjects	8	25	8	6	8	6
Age (yr)	38 (32-43)	36 (33-38)	37 (32-39)	35 (33-37)	34 (30-36)	36 (33-37)
BMI (kg/m²)	23.6 (23-24)	23 (21-25)	23 (21-29)	25 (21-24)	25 (24-27)	23 (21-23)
			23 (20-28)*	24 (20-24)*	25 (23-27)*	23 (21-23)*
Waist to hip ratio	0.77 (0.75-0.81)	0.77 (0.74-0.82)	0.79 (0.76-0.83)	0.77 (0.72-0.82)	0.83 (0.71-1.01)	0.78 (0.72-0.82)
			0.76 (0.74-0.79)*	0.78 (0.71-0.80)*	0.8 (0.70-1.00)*	0.76 (0.07-0.80)*
Fasting insulin (pmol/L)	45 (35-55)†	20 (15-26)†	29 (18-47)	27 (11-48)	32 (20-44)	28 (3-70)
			28 (19-36)*	24 (12-36)*	34 (16-51)*	34 (16-52)*
Fasting glucose (mmol/L)	5.3 (4.1-6.3)	5.2 (4.2-6.2)	5 (4.5-5.6)	4.8 (4.2-5.2)	5 (4.5-5.5)	5 (4.8-5.2)
			5 (4.6-6.4)*	5 (4.3-5.7)*	4.9 (4.5-5.1)*	5.1 (4.5-5.7)*
Fasting cholesterol (mmol/L)	5.3 (5-5.6)	5.4 (4.9-5.9)	5.1 (4.9-5.3)	4.9 (4.2-5.3)	5.1 (4.6-5.8)	5.1 (4.7-5.8)
			5 (4.7-5.3)*	4.9 (4.3-5.4)*	5.1 (4.6-5.5)*	5.3 (4.6-5.3)*
Fasting triglycerides (mmol/L)	0.98 (0.5-1.3)	1.02 (0.61-1.32)	0.87 (0.69-1.34)	1.1 (0.87-1.40)	1.06 (0.86-1.25)	0.92 (0.72-1.18)
			0.86 (0.71-1.00)*	1.04 (0.67-1.40)*	1.01 (0.68-1.34)*	1.01 (0.75-1.34)*

NOTE. Results are expressed as the median with 95% confidence limits.

*Values obtained after the 3-week diet study.

†$P < .05$, PH-CHD *v* control.

the tip of the omentum. Following immediate transfer of the biopsy to the laboratory in Dulbecco's modified Eagle's medium (DMEM) containing 5% bovine serum albumin (BSA), glucose uptake in isolated adipocytes was quantified using modifications to previously described and validated methods.[25-27]

The adipocytes were initially isolated by finely mincing the biopsy and incubating it for 45 minutes in DMEM buffer plus 5% BSA containing collagenase (1 mg/0.5 g tissue) placed in a vibrating water bath at 14 cycles/min. The cells were then filtered through a 400-nm mesh and washed three times in glucose-free Krebs-Ringer phosphate (KRP) buffer with 5% BSA (each wash involving five inversions). At no time were the adipocytes left longer than 5 minutes without agitation. The cells were then left to incubate in the vibrating water bath for a further 2 hours in 95% oxygen–saturated glucose-free KRP buffer with 5% BSA, after which the cells were concentrated. The in vitro studies were then performed on approximately 30,000 isolated adipocytes (≅25 μL), with the cells in the moving water bath throughout. The adipocytes were initially incubated for 45 minutes in 500 μL KRP plus 5% albumin buffer in the presence of 1 nmol/L insulin (described later) before addition of 300 nmol/L nonmetabolized radiolabeled glucose tracer (0.1 μCi 2-deoxy-[U-^{14}C]-D-glucose) and a 15-minute period of incubation before centrifugation through 500 μL silicon oil. Glucose uptake was calculated following liquid scintillation counting of the radiolabeled glucose tracer in the isolated adipocytes. Cells were manually counted in a 1:100 dilution of the cell concentrate with a hemocytometer (with a 200-μm gap), and cell size, diameter, and surface area were measured on 50 cells using a Cue 2 cell counter (Galdi Production, Israel).

To assess glucose uptake with increasing insulin concentrations (0.01 to 10 nmol/L), an insulin dose-response study was performed using subcutaneous and visceral adipocytes taken from 12 women consuming a habitual diet (six controls and six women with PH-CHD).

Adipocyte TNF-α production was measured using a highly sensitive enzyme-linked immunosorbent assay method (Amersham, St Albans, UK) in the adipocyte cell media after 60 minutes of incubation, as previously reported.[11]

In Vivo IS

The low-dose SITT was performed before and after dietary randomization in all 28 women randomized to either a HGI or LGI diet; the second SITT was performed on the day before surgery. The test was performed fasting and consisted of an intravenous bolus of 0.05 U/kg soluble Actrapid insulin (Novo Nordisk, Crawley, UK) in a forearm vein and 3-minute arterialized blood samples taken from the contralateral hand for a total of 15 minutes for plasma glucose and FFAs.[28] Whole-body IS was calculated as the slope of the plasma glucose decrease between 3 and 15 minutes. Plasma FFA suppression during the SITT was analyzed using a Wako calorimetric kit (Wako Chemicals, Hampshire, UK).

Statistics

As a large number of the data sets were not normally distributed, the results are presented as the median with 95% confidence limits. Comparisons between and within groups were made with nonparametric analysis using the Mann-Whitney *U* test and Wilcoxon's signed-rank test where appropriate. The level of significance was taken as P less than .05.

RESULTS

There was no difference in the age, BMI, or waist to hip ratio between women in the different dietary groups or between those with or without PH-CHD. There were no differences in fasting glucose and lipids between the groups, although the women with PH-CHD had higher fasting insulin values than those without PH-CHD when consuming their habitual diet (Table 1).

Dietary details for the women are listed in Table 2. Following randomization to a HGI or LGI diet, the macronutrients of the diet remained unchanged, as did body weight and all fasting biochemical data (Table 1).

In vitro studies in women with and without PH-CHD on all diets showed that subcutaneous cells were larger (cell diameter and surface area) than visceral omental cells (Table 3). The percent increase in glucose uptake above basal stimulated by insulin was consistently less in subcutaneous versus omental adipocytes over the range of insulin concentrations studied (0 to 10 nmol/L; Fig 1a). The percent increase in glucose uptake above basal stimulated by insulin was significantly less for both adipose sites in PH-CHD women versus controls when studied on their habitual diet (median with 95% confidence limits: subcutaneous, 96% (70% to 120%) *v* 28% (17% to 39%); omentum, 113% (83% to 143%) *v* 40% (28% to 52%), $P < .01$). A similar significantly lower percent increase in glucose uptake above basal stimulated by insulin, at insulin doses greater than 0.1 nmol/L, was observed in PH-CHD women compared with controls (Fig 1a and b). This difference in adipocyte IS between controls and women with PH-CHD was observed for both omental and subcutaneous adipocytes (Fig 1b and c).

Among 12 controls randomized to a HGI or LGI diet, there was no difference in the percent increase in glucose uptake above basal stimulated by insulin in either subcutaneous or omental adipocytes (Table 3 and Fig 2a and b). By contrast, 16 women with PH-CHD on a HGI diet had a significantly lower percent increase in stimulated glucose uptake above basal versus women on the LGI diet (subcutaneous, 13% (1% to 29%)

Table 2. Dietary Details for Women With PH-CHD and Controls on The Habitual Diet or After a 3-Week Diet With a HGI or <GI

	Habitual Diet		HGI Diet		LGI Diet	
Nutritional Intake	PH-CHD	Control	PH-CHD	Control	PH-CHD	Control
Energy (kcal)	2,400 (1,900-3,000)	1,900 (1,800-2,300)	2,100 (1,900-2,700)	2,000 (1,800-2,300)	2,200 (1,900-2,500)	2,000 (1,800-2,300)
Energy from carbohydrate (%)	48 (44-53)	51 (44-54)	51 (49-53)	48 (44-54)	53 (46-56)	48 (44-54)
Energy from fat (%)	36 (32-44)	37 (35-43)	37 (32-39)	39 (35-42)	32 (27-35)	37 (32-43)
Nonstarch polysaccharides (g)	18 (16-23)	20 (14-26)	21 (17-22)	17 (15-20)	19 (18-21)	17 (15-19)
Glycemic index	91 (76-98)	88 (84-102)[ab]	87 (76-93)[c]	89 (86-94)[a]	67 (66-73)[c]	71 (57-80)[b]

NOTE. All data were obtained by 7-day diet diaries the week before surgery. Results are expressed as the median with 95% confidence limits. Statistical analysis shows a significant difference between a:a, b:b, and c:c of $P < .05$.

Table 3. Adipocyte Size and Percent Basal Insulin-Stimulated Glucose Uptake in Subcutaneous and Omental Adipocytes From 24 Women With PH-CHD and 37 Controls

	Habitual Diet		HGI Diet		LGI Diet	
In Vitro IS	PH-CHD	Control	PH-CHD	Control	PH-CHD	Control
Subcutaneous adipocytes						
Diameter (μm)	92 (83-102)	90 (50-132)	104 (87-126)[a]	89 (73-110)[a]	120 (98-131)[b]	89 (73-110)[b]
Insulin-stimulated uptake (%)	28 (17-39)[c]	96 (70-120)[c]	13 (1-29)[df]	31 (14-49)[d]	49 (14-49)[ef]	28 (0-50)[e]
Omental adipocytes						
Diameter (μm)	80 (66-94)[g]	56 (52-60)[g]	71 (41-99)[h]	48 (39-56)[h]	75 (41-99)	60 (37-73)
Insulin-stimulated uptake (%)	40 (28-52)[i]	113 (83-143)[i]	44 (4-85)[km]	74 (22-137)[k]	97 (4-86)[lm]	68 (0-2111)[l]

NOTE. Results are expressed as the median with 95% confidence limits. Statistical difference between and within groups a:a to m:m of $P < .05$.

v 49% (20% to 98%), $P < .01$; visceral, 44% (4% to 85%) *v* 97% (47% to 184%), $P < .01$; Fig 2a and b).

While the glycemic index of the diet did not influence TNF-α release in either group of women, TNF-α release was significantly greater in 16 women with PH-CHD versus 12 controls for both subcutaneous and visceral adipocytes (0.3 (0.18 to 0.42) *v* 0.93 (0.39 to 1.30) ng/mL/min and 0.22 (0.15 to 1.30) *v* 0.64 (0.24 to 1.1) ng/mL/min, $P < .04$, respectively; Fig 2c).

Whole-body IS as assessed by the SITT was similar in women with and without PH-CHD (Fig 2d). IS was significantly lower in both groups of women following a HGI versus LGI diet (PH-CHD, 0.14 (0.13 to 0.23 mmol/L/min) *v* 0.31 (0.26 to 0.37), $P < .02$; control, 0.125 (0.09 to 0.21 mmol/L/min) *v* 0.21 (0.1 to 0.23), $P < .05$). However, suppression of plasma FFA concentrations during the SITT was not influenced by the glycemic index of the diet (Fig 2e).

Fig.1a - Dose Ranging Study

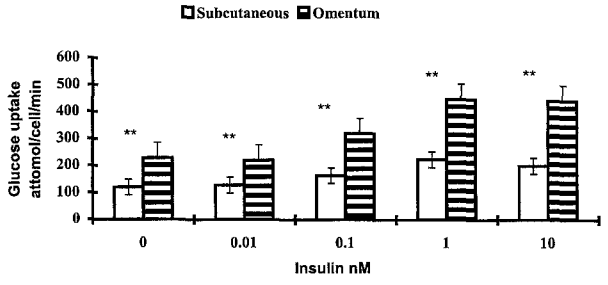

Fig.1b Subcutaneous Adipocytes

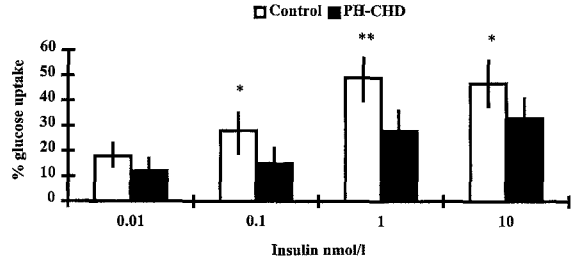

Fig.1c Omental Adipocytes

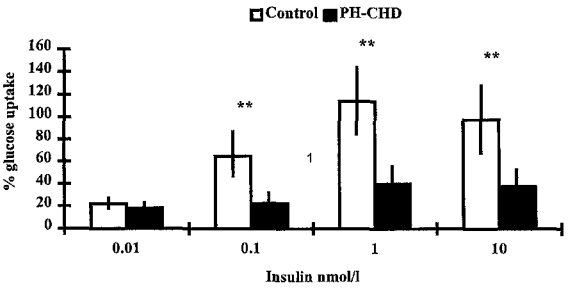

Fig 1. Glucose uptake in subcutaneous and omental adipocytes harvested from women with PH-CHD and without (control). Results are expressed as the median with 95% confidence limits. *$P < .05$, **$P < .01$. (a) Subcutaneous *v* omental cells from control subjects; (b) subcutaneous adipocyte insulin-stimulated glucose uptake for control *v* PH-CHD women; (c) omental adipocyte insulin-stimulated glucose uptake for control *v* PH-CHD women.

DISCUSSION

A family history of CHD and decreased IS are important risk factors for cardiovascular disease.[2,29] CHD is uncommon among premenopausal women, who appear to be metabolically protected.[30] The loss of cardiovascular risk protection in premenopausal diabetic women has been attributed to their decreased IS.[30,31] It is unknown whether decreased IS also contributes to the threefold increased risk of heart disease in women with PH-CHD.[30]

The present report shows functional changes in adipocytes of women with PH-CHD. We observed reduced IS in adipocytes from women with PH-CHD compared with controls, despite no clear difference in whole-body IS. Improvement in the adipocyte IS of women with PH-CHD occurred when the glycemic index of the diet was reduced. LGI versus HGI diet was also associated with improved whole-body IS in both groups of premenopausal women regardless of PH-CHD.

Fasting insulin values were similar in the two groups of women before and after randomization to the study diets; however, higher fasting insulin values were observed in women with PH-CHD versus the controls when consuming their habitual diets. We do not believe that significant differences in whole-body IS likely existed between the women with and without PH-CHD while on their habitual diets, as other surrogate markers of IS, including the BMI, waist to hip ratio, and fasting lipids, were similar. In this study, the SITT was used to assess IS. The SITT has been well validated against the hyperinsulinemic-euglycemic clamp, which remains the gold standard for assessment of IS; the SITT has also been validated against Bergman's minimal model.[28,32] While the SITT provides a reproducible measurement of IS, it does not provide any information on glucose production or turnover, which can be quantified using the other techniques.[32]

In adipocytes of premenopausal women with PH-CHD, we

Fig.2a Subcutaneous Adipocytes

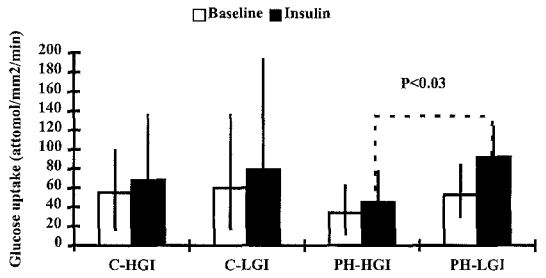

Fig.2b Omental Adipocytes

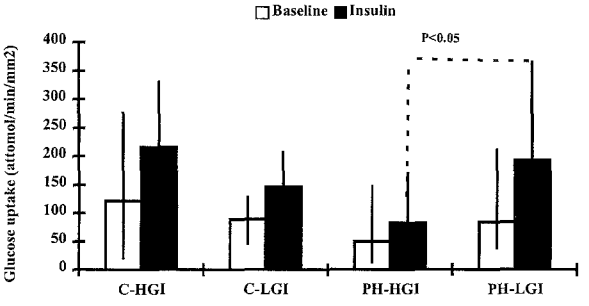

Fig.2c TNF-α Production

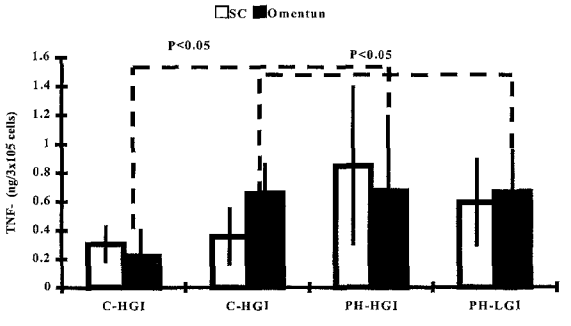

Fig.2d *In vivo* Insulin Sensitivity

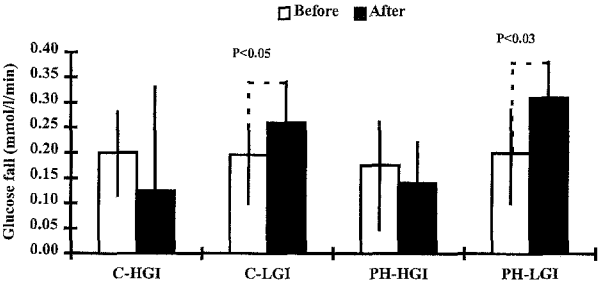

Fig.2e Free Fatty Acid Suppression

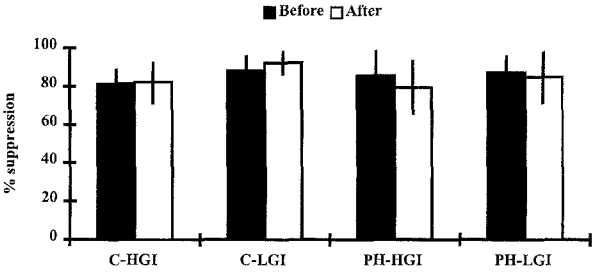

Fig 2. Basal and stimulated glucose uptake (attomol/mm²/min) in subcutaneous (a) and omental (b) adipocytes in 12 controls (C) and 16 women with PH-CHD after 3 weeks of HGI or LGI diet. (c) Subcutaneous and omental adipocyte TNF-α production (ng/3 × 10^5 cells) in 12 controls and 16 women with PH-CHD after a 3-week HGI or LGI diet. (d) In vivo IS assessed by the decrease in plasma glucose (mmol/L/min) during the SITT in 12 controls (C) and 16 women with PH-CHD before and after a 3-week HGI or LGI diet. (e) Plasma FFA suppression (%) during the SITT in 12 controls (C) and 16 women with PH-CHD studied before and after a 3-week HGI or LGI diet.

observed not only the visceral and subcutaneous adipocytes to be more insulin-resistant but also the production of TNF-α to be greater in women with versus without PH-CHD. TNF-α has been implicated in the etiology of other insulin-resistant states through its inhibitory action on phosphorylation of the insulin receptor and insulin receptor substrate-1.[11,33] Recent knockout studies have shown that mice lacking TNF-α are more insulin-sensitive and have lower circulating FFA levels than their wild-type TNF-α counterparts.[34] The present observation of greater adipocyte TNF-α release in women with PH-CHD versus the controls suggests a possible autocrine role for this cytokine in the pathogenesis of insulin resistance in humans.

In the present study on non-obese premenopausal women, omental adipocytes were more insulin-sensitive than the subcutaneous cells, a finding that contrasts with other studies in the literature.[12] The women in this study represent a cohort different from other previously studied groups, being substantially younger, less obese, and healthier. It is possible that omental cells become more insulin-resistant with increasing age and body weight; in addition, they may be more responsive to adverse environmental factors than subcutaneous cells. The idea that dietary factors may play a role in determining visceral adipocyte IS is suggested by the observation that the IS of visceral adipocytes was similar to that of subcutaneous cells when the women with PH-CHD were consuming a HGI diet. It also remains a possibility that IS in adipocytes is site-specific, being influenced by local autocrine and paracrine factors that change with age.

A family history of insulin-resistant syndromes may be associated not only with inheritable metabolic differences in adipocyte IS but also with environmental and life-style factors that promote abdominal obesity and therefore further aggravate insulin resistance and cardiovascular risk. Women with PH-CHD may inherit a metabolic vulnerability to abdominal obesity together with an environmental life-style pattern that, when combined, increase both insulin resistance and the risk of CHD.

Despite previous studies showing an inverse relationship between insulin-stimulated glucose uptake and FFA release in isolated adipocytes,[25] no difference in suppression of circulating plasma FFA to insulin was observed in women with and without PH-CHD. However, since supraphysiological concentrations of insulin are achieved during the SITT and since hormone-sensitive lipase is totally suppressed at insulin concentrations

well below those that decrease blood glucose, it is unlikely that subtle differences in adipocyte IS and FFA release can be detected by this method.[28]

Following a 3-week diet containing a high proportion of LGI carbohydrates, whole-body IS increased in both groups of women. This occurred despite no significant decrease in fasting glucose or insulin concentrations. The measurement of in vivo IS by the SITT assesses both insulin's ability to suppress hepatic glucose output and peripheral glucose uptake, the latter being predominately into muscle, which accounts for 80% of glucose uptake. The improvement in IS in the control women following a LGI diet may have occurred in muscle, as no improvement in in vitro adipocyte sensitivity was found. In women with PH-CHD, the increase in adipocyte IS following a LGI diet may have contributed to the increase in IS. This would theoretically happen if FFA release into the portal circulation was decreased as hepatic glucose production decreased, so increasing in vivo IS as assessed by the SITT.

This study demonstrates that a LGI diet effectively restores IS in both visceral and subcutaneous adipocytes in women with PH-CHD. Similar dietary modification has been shown to improve IS in subjects with CHD,[8] NIDDM,[9] and obesity.[10] A previous study in healthy subjects has shown that substitution of dietary carbohydrate with slowly absorbed carbohydrates is associated with decreased hyperinsulinemia and greater suppression of FFA postprandially,[35] in addition to a decrease in fasting hepatic glucose output. Similar metabolic benefits are found with the consumption of frequent small regular meals as opposed to less frequent larger meals.[36,37] LGI diets achieve lower and attenuated insulin responses postprandially that effectively suppress FFA release longer. By contrast, HGI carbohydrates tend to cause a high peak insulin concentration, which can result in a precipitous decrease in blood glucose below basal values with a corresponding increase in counterregulatory hormones that decrease IS.[16]

The present short-term study complements recent epidemiological studies that show long-term LGI diets reduce insulin demands and improve IS,[21] reducing the risk of NIDDM in healthy men and women.[19,20]

This study provides a scientific basis for the observational studies that a LGI diet is beneficial to the health of premenopausal women. The cardiovascular significance of the metabolic differences in adipocyte IS and TNF-α production in women with PH-CHD needs to be further elucidated. Whether a diet high in slowly absorbed carbohydrate can normalize the IS of adipocyte cells in these women and thereby reduce their overall risk of heart disease remains to be determined.

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