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Effect of postprandial insulinemia and insulin resistance on measurement of arterial stiffness (augmentation index)

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Abstract

Background: Arterial stiffness, specifically augmentation index (AIx), is an independent predictor of cardiovascular risk. Previous studies suggest that insulin infusion decreases AIx and that this response is attenuated in insulin resistance. Whether physiological postprandial insulinemia similarly affects AIx measurements, and whether insulin resistance modifies this response, has not been studied.
Methods: Seven relatively insulin-resistant and seven insulin-sensitive postmenopausal women received low-carbohydrate and high-carbohydrate high-fat meals on separate days. Glucose and insulin levels were measured for 360-min following meal consumption. AIx was measured by radial artery applanation tonometry at regular intervals postprandially.
Results: Postprandial increases in glucose and insulin were greater following the high-carbohydrate high-fat meal in both insulin-sensitive and insulin-resistant subjects. AIx decreased in both groups following both meals. In insulin-sensitive subjects, the postprandial reduction (incremental area above the curve) in AIx was greater following the high-carbohydrate vs. low-carbohydrate high-fat meal (-6821 ± 1089 vs. -3797 ± 1171%·min, respectively, $P = 0.009$). In contrast, in insulin-resistant subjects, postprandial AIx responses were similar following the meals, suggesting that insulin resistance is associated with impaired postprandial arterial relaxation.
Conclusions: This study demonstrates that the carbohydrate content of a meal, and, hence, the magnitude of the postprandial glucose and insulin responses it elicits, are important determinants of postprandial AIx measurements. The further observation that insulin resistance modified this effect raises the possibility that this phenomenon is a contributor to increased cardiovascular risk in insulin resistance. The results indicate that future studies of AIx need to control for the effects of these potentially confounding variables and that measurement of AIx should be standardized with respect to meals.

Keywords: Arterial stiffness; Augmentation index; Insulin resistance; Postprandial state

1. Introduction

Systemic arterial stiffness, or reduced compliance, is a validated, independent predictor of cardiovascular mortality [1,2]. Although various indices of large arterial stiffness are described, there has been considerable interest in 'augmentation index' (AIx), which is determined by pulse wave velocity (PWV) and the site of reflection of the transmitted aortic pressure wave [3,4]. AIx is derived non-invasively by applanation tonometry of the radial, carotid or femoral arteries [5–7]. It is associated with coronary risk [8,9] and angiographically proven coronary artery disease [10] and is an independent predictor of total and cardiovascular mortality in high-risk patients, such as those with end-stage renal failure [2].

Previous results suggest that the measurement of AIx may be affected by nutrient intake. In a study of postmenopausal women, we recently reported that AIx decreased postprandially and that the reduction was proportional to the carbohydrate content of the meal, and hence, the magnitude of the glucose and insulin responses it elicited [11]. Extrapolation from studies using the hyperinsulinemic–euglycemic clamp technique [12] suggests that insulin, rather than glucose, is the main determinant of arterial stiffness in the postprandial state.

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Insulin resistance has been shown to attenuate insulin's dilatory effect on AIx [13], suggesting that insulin resistance modifies the relationship between insulin and central hemodynamic function. In some, but not all studies [14], measures of insulin resistance were reportedly unrelated to basal or 'unstimulated' measures of systemic arterial stiffness, such as AIx [15,16] and PWV [17]. In contrast, significant associations between insulin resistance and localized measures of arterial compliance and distensibility have been observed [18–20], although relationships were confined to a particular artery [18,19] or, in some cases, were gender specific [18]. However in modern times, humans spend the majority of the day in the postprandial state, which has been proposed to be proatherogenic and may contribute to the development of atherosclerosis [21]. Therefore, the negative basal findings reported in some studies do not exclude the possibility that insulin resistance is associated with a dynamic abnormality in, or impairment of, 'insulin stimulated' postprandial arterial relaxation.

The aims of this study were to determine the impact of physiological postprandial endogenous hyperinsulinemia on AIx measurements and whether these responses are modified in insulin resistance. Meal studies, particularly those that specifically control for the amount of carbohydrate, provide an appropriate study design by which the effect of physiological hyperinsulinemia on arterial stiffness can be examined.

2. Materials and methods

2.1. Subjects

Eighteen postmenopausal females were recruited via advertisements in local newspapers, on the St. Vincent's Hospital campus and at public seminars conducted at the Garvan Institute of Medical Research. We specifically recruited older postmenopausal women as this is a group at significant cardiovascular risk. Data on 10 of the 18 subjects included in this cohort was ascertained as part of a previous meal study performed in our research facility [11]. Smokers, heavy drinkers, subjects with known type 2 diabetes or ischemic heart disease and those treated with lipid-lowering agents or hormone replacement therapy were excluded. Insulin resistance was estimated by homeostasis model assessment (HOMA-R) [22]. HOMA-R scores from the two meal study days were averaged for each subject. Four subjects with HOMA-R scores at or close to the median of the group were excluded from further analyses to ensure clear separation of the groups. The remaining 14 subjects were classified as relatively insulin-resistant (7 subjects with HOMA-R above median: range 2.6–4.8, in whom fasting insulin was >10 mU/L) or insulin-sensitive (7 subjects with HOMA-R below median: range 1.4–2.1, in whom fasting insulin was <10 mU/L), consistent with previous reports [23]. Two subjects with fasting plasma glucose levels >6 mmol/L underwent a standard 75 g oral glucose tolerance test following completion of the study; one had normal glucose tolerance and the other impaired glucose tolerance according to American Diabetes Association criteria [24]. The one subject in the insulin-sensitive group taking irbesartan 150 mg daily and the one subject in the insulin-resistant group taking ramipril 10 mg daily continued their anti-hypertensive medications throughout the study period. The study was approved by the Research Ethics Committee of St. Vincent's Hospital. All subjects provided written informed consent.

2.2. Experimental protocol

Two meal studies were conducted on separate days approximately 1 week apart: a low-carbohydrate high-fat meal (~1084 kcal, consisting of 85 g of fat, 45 g of protein and 23 g of carbohydrate) was consumed during visit 1 and a high-carbohydrate high-fat meal (~1385 kcal, consisting of 88 g of fat, 37 g of protein and 104 g of carbohydrate) was consumed during visit 2. No food or drink was allowed from 2200 the night before each study. The two subjects taking a morning dose of single antihypertensive agent took their medication at the completion of each study.

Subjects arrived at the Clinical Research Facility, Garvan Institute of Medical Research, between 0800 and 0830 having refrained from vigorous exercise and alcohol for 48 h prior to each visit. An intravenous cannula was inserted into a large antecubital vein for blood sampling and was kept patent by infusion of 0.9% saline (~120 ml/h). Subjects remained supine for the duration of the study. After a 15-min rest, fasting samples were taken for plasma glucose, serum insulin, total and HDL cholesterol, triglycerides and non-esterified fatty acids. Repeat samples were collected before the meal was consumed; the two baseline samples were averaged when calculating incremental areas under the curve (iAUC). Baseline fasting duplicate AIx measurements were recorded and averaged in analyses. The meal was then consumed over 20–30 min. No other food or drink was allowed following the meal apart from 600 ml of water over the course of the 6-h study. Repeat blood samples were taken 30, 60, 90, 120, 180, 240, 300 and 360 min following the end of the meal (t=0 min). Repeat duplicate AIx measurements were performed immediately after the last mouthful of food and at the time points listed above. All measurements were recorded by a single investigator (JRG), who was blinded to each subject's insulin sensitivity. Subjects underwent dual-energy X-ray absorptiometry scanning at the end of one of the two study days as described below.

2.3. Applanation tonometry

An Automatic Oscillometric Digital Blood Pressure Monitor (OMRON HEM-705CP, OMRON Corp., Tokyo,

Japan) was used to measure blood pressure with the subject supine at ~45°. Applanation tonometry of the radial artery was performed using a highly sensitive transducer (SyphgomoCor®, AtCor Medical, Sydney), which yields waveforms comparable to tracings derived from catheter studies [25]. The central arterial waveform was derived from the peripheral waveform using a validated transfer function [26]. AIx was calculated by dividing the difference between the second systolic peak and the diastolic pressure by the difference between the first systolic peak and the diastolic pressure (×100%) as previously described [27]. We have previously reported that the day-to-day coefficient of variation for repeated fasting measurements of AIx on four separate days is 5.3% in our hands [11].

2.4. Anthropometry and dual-energy X-ray absorptiometry

Weight and height were measured in a hospital gown. Body mass index was calculated by dividing weight by height squared (kg/m^2). Waist circumference was measured as the widest circumference between the lower end of the ribs and the anterior superior iliac spines.

Dual-energy X-ray absorptiometry was used to measure body composition according to a three-compartmental model, comprising fat mass, lean tissue and bone mineral content (Lunar DPX GE-Lunar instrument, Madison, WI). Total body fat was expressed in absolute terms (kilograms) and as a percentage of total body mass. Central abdominal fat was calculated as previously described by our group [28]. Fat-free mass was defined as the sum of lean tissue and bone mineral content. As previously published, the coefficients of variation for repeated dual-energy X-ray absorptiometry measurements on four separate occasions in 10 subjects are: total body fat mass, 2.9%; fat-free mass, 1.4%; central abdominal fat (kg), 5.8%; and percentage central abdominal fat, 5.1% [28].

2.5. Analytical methods

Plasma glucose was measured immediately by the glucose oxidase method (Yellow Springs Instruments Model 2300 STAT PLUS 230 V, YSI Inc., Yellow Springs, OH) and insulin by radioimmunoassay (Linco Research, St Charles, MI). Serum lipids (total cholesterol, HDL cholesterol and triglycerides) and non-esterified fatty acids were determined spectophotometrically by enzymatic colorimetry at 490 nm (Roche Diagnostics, Basel, Switzerland) and 550 nm (Wako Inc., Osaka, Japan) respectively. Inter-assay and intra-assay coefficients of variation were <10% in our laboratory.

2.6. Statistical methods

Data are mean ± standard error (S.E.) unless otherwise stated. Postprandial incremental area under the curve (iAUC) was calculated using the trapezoidal method by subtracting baseline values extrapolated over 390 min (30-min basal period and 360-min postprandial period) from the total postprandial area. Analysis of variance (normally distributed data) and Mann–Whitney *U*-tests (skewed data) were used to compare baseline characteristics between insulin-sensitive and insulin-resistant subjects. Paired *t*-tests (normally distributed data) and Wilcoxon signed rank tests (skewed data) were used to compare results following the two meals on the same subject. Analyses were performed using Statview 5.0 (SAS Institute, Cary, NC). $P<0.05$ was deemed statistically significant.

3. Results

Baseline body composition, biochemical and hemodynamic characteristics of the study cohort are shown in Table 1. As expected, insulin-resistant subjects had greater total fat and central abdominal fat masses than insulin-sensitive subjects, although these differences failed to reach statistical significance ($P=0.12$ and $P=0.08$, respectively), due, most likely, to the size of the insulin-sensitive and insulin-resistant subgroups. Results were similar after adjusting for age (data not shown). Although baseline AIx values tended to be higher in insulin-sensitive subjects ($P=0.13$), there was no significant difference between the groups after adjusting for age ($P>0.52$).

Table 1
Baseline characteristics

Variable	Insulin-sensitive subjects ($n=7$)	Insulin-resistant subjects ($n=7$)
Age (years)	68.9±5	62.9±4.9†
Weight (kg)[a]	63.7±9.9	77.5±19.9
Body mass index (kg/m^2)[a]	24.7±2.6	29.6±4.8†
Waist circumference (cm)	79.6±8.5	96.4±20
Total body fat (kg)	24.4±7.8	33.4±11.6
Total body fat (%)	39.6±6.6	43.1±8.8
Central abdominal fat (kg)	1.5±0.5	2.4±1.1
Central abdominal fat (%)	34.3±8.0	40.2±10
Fat free mass (kg)	38.1±3.0	45.0±10.9
Fasting glucose (mmol/L)[a]	5.07±0.32	5.27±0.63
Fasting insulin (mU/L)[a]	8.31 (7.04–9.29)	15.28 (13–20.73)††
HOMA-R	1.84±0.1	3.79±0.34§
Fasting cholesterol (mmol/L)[a]	5.58±1	5.46±1.11
Fasting HDL cholesterol (mmol/L)[a]	1.57±0.45	0.93±0.24†
Fasting triglycerides (mmol/L)[a]	0.74 (0.69–1.13)	1.32 (0.73–1.4)
Fasting NEFAs (mmol/L)[a]	0.58±0.24	0.54±0.12
Aortic systolic blood pressure (mm Hg)[a]	127±10	119±11
Aortic diastolic blood pressure (mm Hg)[a]	82±6	83±6
AIx (%)[a]	163±10	155±10

Values are mean±S.D or median (interquartile range). NEFA: non-esterified fatty acid.
[a] Average of baseline values from both visits.
† $P<0.05$ compared to insulin-sensitive subjects.
†† $P<0.005$ compared to insulin-sensitive subjects.
§ $P<0.0005$ compared to insulin-sensitive subjects.

3.1. Effect of insulin resistance on postprandial glucose, insulin and lipid levels

Postprandial increases in glucose and insulin were greater following the high-carbohydrate high-fat meal in both insulin-sensitive and insulin-resistant subjects (Fig. 1a and b). No significant differences between the meals were found in either insulin-sensitive or insulin-resistant subjects in postprandial total cholesterol, HDL cholesterol, triglyceride or non-esterified fatty acid responses (data not shown).

3.2. Effect of insulin resistance on postprandial central hemodynamic measures

The effect of meal consumption on aortic systolic and diastolic blood pressure is shown in Fig. 2a and b. Postprandial changes in AIx are demonstrated in Fig. 2c. AIx decreased following both meals in both insulin-sensitive and insulin-resistant subjects. Postprandial changes in AIx were not significantly associated with baseline measures of insulin resistance or body composition in either group (data not shown).

In insulin-sensitive subjects, the postprandial reduction in AIx (iAUC) was significantly greater following the high-carbohydrate high-fat meal (−6821±1089 vs. −3797±1171%·min, high- vs. low-carbohydrate high-fat meal, respectively, $P=0.009$), implying greater systemic arterial relaxation following the former (which also elicited greater postprandial glucose and insulin responses). Of note, the difference in AIx between the low- and high-carbohydrate high-fat meals was evident as early as 90 min after meal consumption. There was no significant difference between the meals in the postprandial increase in heart rate in insulin-sensitive subjects (iAUC, $P=0.49$).

In insulin-resistant subjects, despite marked postprandial hyperinsulinemia (relative to insulin-sensitive subjects), the magnitude of the postprandial reduction in AIx (iAUC) following the high- and low-carbohydrate high-fat meals was similar (−5584±1574 vs. −3834±1045%·min, respectively, $P=0.33$, Fig. 2c). As postprandial increases in heart rate were greater following the high-carbohydrate high-fat meal (average difference 4 beats/min; iAUC high- vs. low-carbohydrate high-fat meal, $P=0.02$), fasting and postprandial AIx values were normalized to a heart rate of 75 beats/min; however, results were unchanged (AIx iAUC, high- vs. low-carbohydrate high-fat meals, $P=0.44$). A similar finding was observed when the postprandial AIx response following the high-carbohydrate high-fat meal in insulin-resistant subjects was compared to that following the low-carbohydrate high-fat meal in insulin-sensitive subjects, with no significant difference between these responses (iAUC, $P=0.38$).

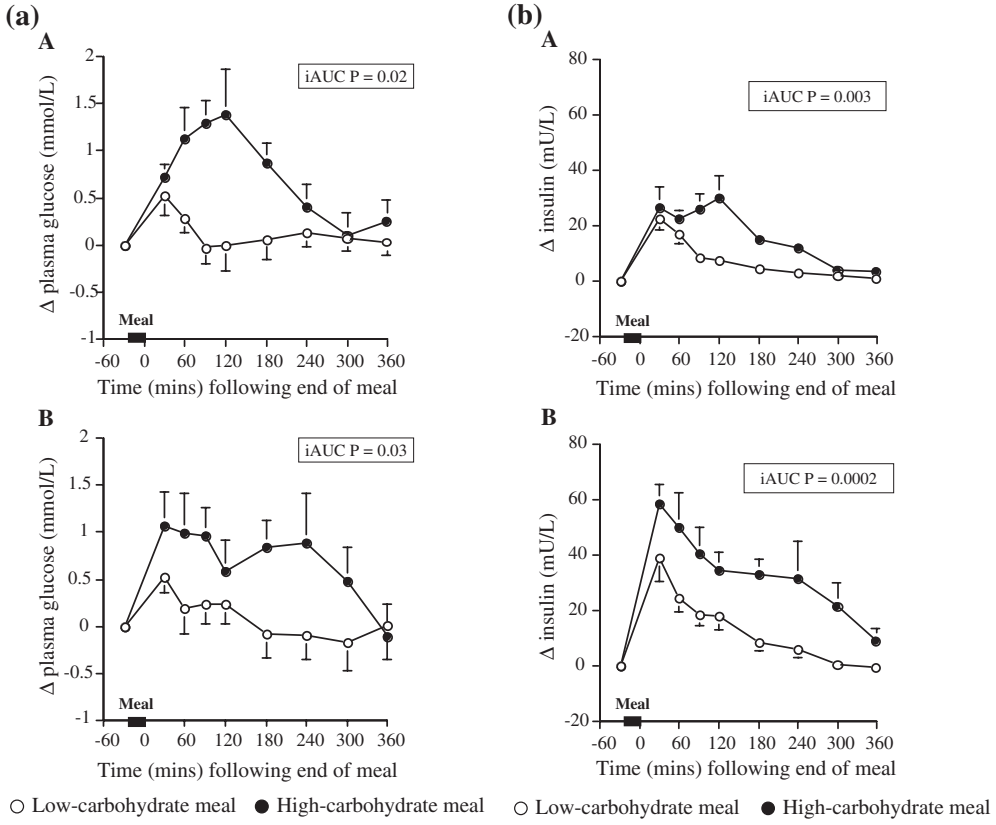

Fig. 1. (a) Incremental change in plasma glucose levels following low- and high-carbohydrate high-fat meals in insulin-sensitive (A) and insulin-resistant (B) subjects. Data are mean±S.E. (b) Incremental change in insulin levels following low- and high-carbohydrate high-fat meals in insulin-sensitive (A) and insulin-resistant (B) subjects. Data are mean±S.E.

4. Discussion

The current study was designed: (i) to examine whether the differing glucose and insulin responses elicited from low- and high-carbohydrate meals had differential effects on postprandial levels of AIx; and (ii) to determine the influence of insulin resistance on these responses. In contrast to previous studies investigating the effect of insulin on arterial stiffness, the novel study design used in this report more closely reflects daily physiological meal-related fluctuations in insulin levels that are typical of modern-day society. As previously reported by our group [11], we found that AIx decreased in the postprandial state following both the low-carbohydrate and high-carbohydrate high-fat meals. This finding validates a recent recommendation that the measurement of arterial stiffness should be undertaken under standardized conditions in relation to meals (ideally fasting) [29]. Postprandial changes in aortic systolic blood pressure paralleled the postprandial reduction in AIx observed in our study. As blood pressure is regarded as an important determinant of arterial stiffness, changes in blood pressure may have contributed, at least in part, to the decrease in arterial stiffness following the meals [29]. However, the temporal association between these changes suggests the possibility of similar underlying physiological mechanisms modulating both blood pressure and AIx in the postprandial state.

In insulin-sensitive subjects, the greater glucose and insulin responses following the high-carbohydrate high-fat meal were associated with greater postprandial reductions in AIx. Although we are unable to distinguish between the effects of insulin and glucose on postprandial arterial stiffness in the current study, a recent hyperinsulinemic–euglycemic clamp study demonstrated that AIx decreased rapidly during sequential supraphysiological insulin infusions, despite stable plasma glucose levels [12]. This result suggests that insulin is likely to be the predominant effector of reductions in large artery stiffness in the current study.

That physiological endogenous insulinemia may affect postprandial AIx is biologically plausible. Large artery stiffness or compliance is determined by its structural components and functional properties. To a degree, the latter is mediated by smooth muscle tone, which is regulated by endothelial nitric oxide (NO) bioavailability [3]. The importance of NO synthesis in regulating AIx was demonstrated by a recent study by Wilkinson et al., which found that pharmacological inhibition of NO synthase

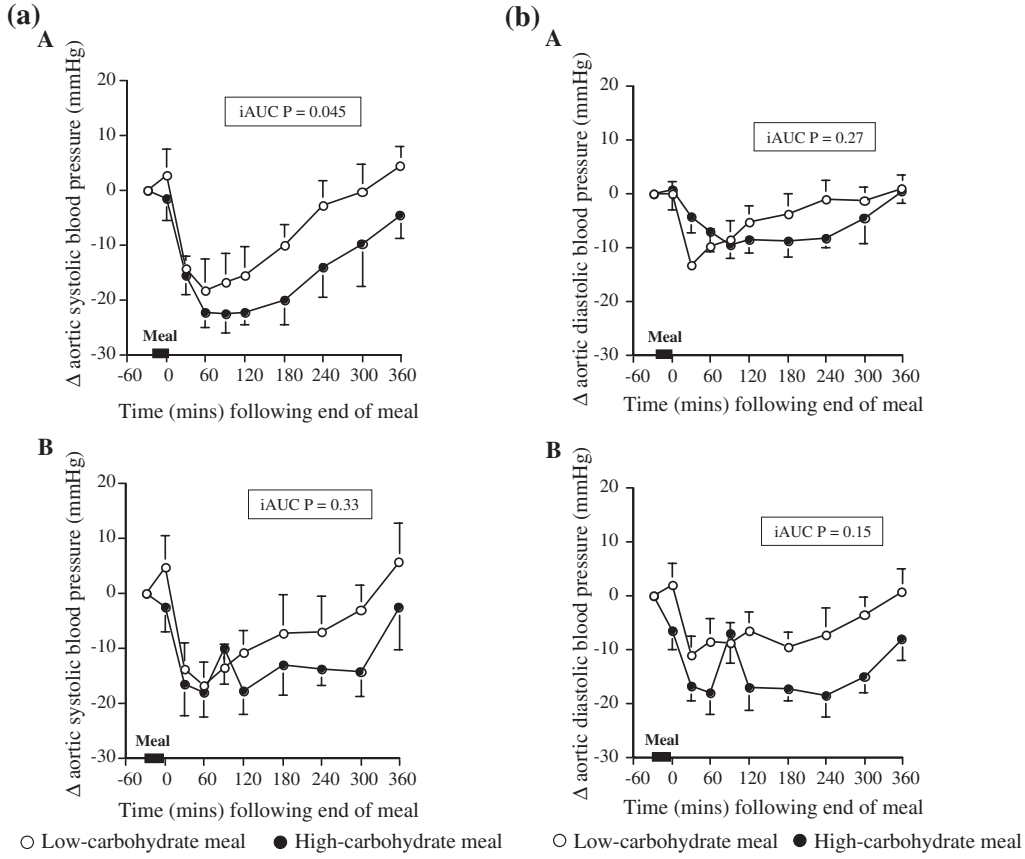

Fig. 2. (a) Incremental change in aortic systolic blood pressure following low- and high-carbohydrate high-fat meals in insulin-sensitive (A) and insulin-resistant (B) subjects. Data are mean±S.E. (b) Incremental change in aortic diastolic blood pressure following low- and high-carbohydrate high-fat meals in insulin-sensitive (A) and insulin-resistant (B) subjects. Data are mean±S.E. (c) Incremental change in Augmentation Index following low- and high-carbohydrate high-fat meals in insulin-sensitive (A) and insulin-resistant (B) subjects. Data are mean±S.E.

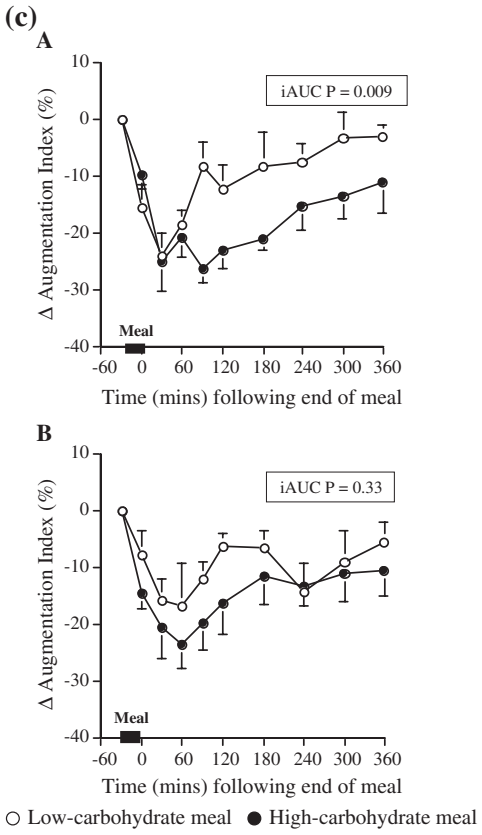

Fig. 2 (*continued*).

resulted in a dose-dependent increase in AIx [3]. Although insulin has been shown to exert its vasodilatory effect on peripheral resistance vessels by increasing NO release [30], whether insulin's effect on large artery stiffness is also mediated via a NO dependent mechanism is less clear [16].

In insulin-resistant subjects, despite greater postprandial increases in insulin levels relative to insulin-sensitive subjects, postprandial reductions in AIx were similar following the high- and low-carbohydrate high-fat meals, suggesting resistance to postprandial 'insulin-stimulated' arterial relaxation. Our results are consistent with a previous study, which reported that insulin infusion reduced AIx in non-obese insulin-sensitive subjects, but that this reduction was delayed and impaired in obese insulin-resistant subjects [13]. In another study from the same group, insulin-induced changes in AIx were significantly related to a number of components of the Metabolic Syndrome, including glucose infusion rate during hyperinsulinemic–euglycemic clamp and waist-to-hip ratio [16]. As basal AIx is an independent predictor of cardiovascular risk and mortality [2,8–10], and humans spend most of the day in the postprandial state, failure to reduce arterial stiffness in response to postprandial hyperinsulinemia throughout the day may have physiological relevance in relation to cardiovascular risk. Although the clinical implications of our findings remain speculative, it is possible that the early demonstration of impaired insulin-induced arterial relaxation may help identify insulin-resistant subjects who would benefit most from cardiovascular risk reduction.

Insulin resistance is associated with impaired NO synthase activity and reduced NO production [31,32]. If insulin indeed mediates large artery compliance via a NO-dependent mechanism, this raises the possibility that impaired NO production may contribute to the blunted AIx response observed in insulin-resistant subjects in our study. Alternatively, insulin resistance per se may have a direct inhibitory effect on insulin-mediated relaxation of large arteries. Similarities in the insulin signalling pathway in endothelial and muscle cells make a dual defect in insulin signalling, affecting glucose transport in the muscle cell and NO production in the endothelial cell, biologically plausible [31,33].

Our study has potential limitations. First, our data are cross-sectional. Second, to avoid the influence of gender on arterial stiffness, the study population was limited to postmenopausal women; therefore results may not be applicable to younger women or men. Third, the limited sample sizes in subgroup analyses may have limited our ability to detect a difference in postprandial AIx responses between the meals in insulin-resistant subjects; however, the finding of a significant difference in insulin-sensitive subjects would argue against this.

This study demonstrates that the carbohydrate content of a meal, and, most likely, the magnitude of the insulin response it elicits are important determinants of postprandial AIx measurements. As a difference in AIx was not apparent in the fasting state, this study further reinforces the importance of extending investigation of cardiovascular risk factors into the postprandial state. Our findings also illustrate the importance of standardizing the meals used to examine postprandial metabolic variables, as failure to control specifically for the amount of carbohydrate in the meal may have confounded interpretation of the effect of postprandial insulinemia on arterial stiffness. The finding that insulin resistance further modified the postprandial AIx response indicates that future studies are necessary to determine the role (if any) of this novel postprandial effect of insulin resistance in atherosclerosis.

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