Evaluation of the FIRI (Fasting Insulin Resistance Index) and selected plasma parameters associated with insulin resistance as predictors of cardiovascular mortality in rural Chinese women

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Insulin Resistance Syndrome (IRS) refers to a cluster of pathologies including hypercholesterolaemia, diabetes, hypertension and cardiovascular disease indicating that these diseases share a common aetiology in insulin resistance and hyperinsulinaemia. Recently a simple index of insulin resistance referred to as the Fasting Insulin Resistance Index (FIRI) was proposed by Duncan *et al*, for use in clinical practice and epidemiologic investigations of disease FIRI is estimated as the product of fasting plasma glucose and fasting plasma insulin divided by 25 (FIRI = (glucose x insulin/25). This communication evaluates the utility of FIRI using data from a large comprehensive ecologic study on diet and disease in rural counties in the People's Republic of China and provides support for the use of this biomarker/index in epidemiologic studies on disease states associated with IRS.

Key words: Insulin resistance, FIRI (Fasting Insulin Resistance Index), cardiovascular disease, mortality, Chinese, women, biomarkers, SMBG (sex hormone binding globulin), lipids, hypertension, glucose, stroke, myocardial infarction

Introduction

The pathogenesis of coronary heart disease and hypertensive heart disease have been proposed to be part of a larger cluster of pathologies described by GM Reaven in 1988 as the Insulin Resistance Syndrome (IRS)[1]. In a recent review of the literature, GM Reaven cites substantial evidence suggesting that IRS is likely a combination of insulin resistance and subsequent compensatory hyperinsulinaemia -- common denominator mechanisms for the pathogenesis of hypercholesterolemia, diabetes, hypertension, and cardiovascular disease (CVD)[2]. The most widely recognised plasma parameters associated with increased risk for IRS include: low levels of HDL cholesterol and sex hormone binding globulin (SHBG)[3], and elevated levels of fasting insulin, triglycerides, and plasma urate[2].

More recently, Duncan *et al* have proposed a simple measure of insulin resistance for use in clinical or epidemiological studies[4]. This empirically derived parameter, referred to as the Fasting Insulin Resistance Index (FIRI), is estimated as the product of plasma insulin and glucose (FIRI= fasting glucose x fasting insulin/25).

This communication evaluates FIRI and the commonly cited plasma parameters associated with IRS as predictors of CVD mortality (hypertension, stroke, and myocardial infarction), using data from a large comprehensive ecologic study conducted in the People's Republic of China in 1983[5]. Other risk factors linked to these cardiovascular mortalities, and therefore included in the analyses, are dietary salt intake[6], smoking[7], and BMI (body mass index)[8].

Subjects and methods

Details of the methods and procedures used in this study have been reported elsewhere[3]. In 1983, an ecologic survey was conducted in 65 widely dispersed counties in the People's Republic of China. The information collected included the intakes of foods and nutrients measured for households, levels of various blood and urinary constituents assayed in pooled samples, questionnaire-based information on lifestyle and frequency of intakes of selected food categories for individual subjects. Individual plasma samples were pooled by sex, age (35-44 y, 45-54 y, and 55-64y) and commune to assess the relation between biochemical characteristics and disease-specific mortality rates at the county level. Thus, all data analysed herein represent county means. Validation studies show excellent agreement between pooled plasma values and the average of the values for the individual samples comprising that pool.

Statistics

A computerised statistical software package (SAS) was used for all the statistical analyses (including all descriptive and analytical measures) reported here[5]. Of the 65 counties originally surveyed, only 48 had CVD mortality data and thus were retained for this study. Mean county cardiovascular mortality rates (n=48) for women 0-64 years of age were analysed as the dependent variables. The

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independent variables included in the analysis reported here were selected on the basis of demonstrated biological relevance and include SHBG, HDL cholesterol, triglycerides, body mass index, smoking habits and dietary salt intake. Additionally, a recently proposed index of insulin resistance, FIRI, was also included as per the formula put forward by Duncan *et al*: FIRI = glucose x insulin/25. This approximates the parameter defined by Matthews *et al* (insulin resistance = insulin/$22.5^{-Ln\ glucose}$)[9].

Correlation analyses were used to examine the magnitude, direction and significance of the association of CVD mortality rates with selected plasma and anthropometric variables related to insulin resistance syndrome (data not shown).

Multiple regression analyses were then used to further explore the relationship between mortality and selected indicators of insulin resistance. The hypothesised primary biochemical predictors of insulin resistance (SHBG, HDL cholesterol, triglycerides, and FIRI) were examined for three different categories of cardiovascular mortality: stroke, hypertension, myocardial infarction. The possible effects of other confounding factors (body mass, total cholesterol, smoking, and dietary salt intake) were controlled for in the model.

Results

The county means for age in this sample of rural Chinese women ranged from 35 to 64 y (mean = 48.7 y). The county mean for the body mass index ranged from 18.5 to 23.0 kg/m^2 (mean = 20.6 kg/m^2). The county average percentage of Chinese women who ever smoked any form of tobacco for more than 6 months ranged from 0% to 68.3% (mean = 13%).

FIRI was negatively correlated with HDL cholesterol ($r = -0.32$, $p<0.01$) and SHBG ($r = -0.34$, $p<0.01$); FIRI was positively correlated with BMI ($r = 0.27$, $p<0.05$) and smoking ($r = 0.40$, $p<0.001$). No relation with this parameter was observed for triglycerides, glucose, total cholesterol, or uric acid. Fasting insulin paralleled FIRI's correlations in both significance and direction. SHBG was negatively correlated with triglycerides ($r = -0.52$, $p<0.001$), insulin ($r = -0.37$, $p<0.01$), BMI ($r = -0.41$, $p<0.001$) and salt intake ($r = -0.36$, $p<0.01$). There were no significant correlations with either uric acid or glucose and any other IRS biomarker.

Standardised regression coefficients for selected insulin resistance biomarkers are presented in Table 1 adjusted for total cholesterol, BMI, smoking, and dietary salt intake. For myocardial infarction, unadjusted levels of insulin and FIRI are equally significant positive biomarkers ($\beta = 0.43$, $P<0.01$). Unadjusted for other possible confounding factors, SHBG was the strongest negative biomarker ($p = -0.43$, $P<0.01$). After adjustment, FIRI was only a slightly stronger predictor of myocardial infarction compared to insulin ($p = 0.36$ and $p = 0.33$ respectively). Significant biomarkers related to hypertensive heart disease were glucose ($p = 0.37$, $P<0.01$) and triglycerides ($p = 0.42$, $P<0.01$) controlling for other covariates in the statistical model. None of the selected plasma indicators demonstrated a significant relationship with mortality for stroke. Neither uric acid nor HDL cholesterol were significant biomarkers for cardiovascular disease in any of the regression analyses.

Table 1. Standardised regression coefficients for selected predictors of insulin resistance for selected cardiovascular mortalities unadjusted and adjusted for total cholesterol, BMI, smoking and dietary salt intake.

Mortality Rate	Myocardial Infarction		Hypertensive Heart Disease		Stroke	
	b	R^2	b	R^2	b	R^2
Covariate						
HDL cholesterol						
unadj	0.01	[0.00]	0.00	[0.00]	0.00	[0.00]
adj	-0.02	[0.26]	-0.02	[0.17]	-0.08	[0.21]
SHBG						
unadj	0.43	[0.18]**	-0.33	[0.11]*	-0.40	[0.16]**
adj	-0.29	[0.35]*	-0.20	[0.21]	-0.29	[0.26]
Insulin						
unadj	0.43	[0.18]**	0.19	[0.04]	0.29	[0.08]*
adj	0.33	[0.30]*	0.10	[0.16]	0.25	[0.23]
Glucose						
unadj	0.18	[0.03]	0.31	[0.09]*	0.14	[0.02]
adj	0.24	[0.29]	0.37	[0.28]**	0.14	[0.21]
Triglycerides						
unadj	0.31	[0.10]*	0.43	[0.19]**	0.11	[0.01]
adj	0.29	[0.32]	0.42	[0.31]**	-0.04	[0.20]
Uric acid						
unadj	0.00	[0.00]	0.22	[0.05]	0.08	[0.01]
adj	0.04	[0.25]	0.26	[0.22]	0.11	[0.20]
FIRI'						
unadj	0.43	[0.19]**	0.29	[0.08]*	0.32	[0.10]*
adj	0.36	[0.32]*	0.27	[0.19]	0.29	[0.23]

aFIRI = Fasting Insulin Resistance Index = glucose x insulin/25
* $p<0.05$ ** $p<0.01$ *** $p<0.001$

Conclusion

Reports on the use of FIRI as a reasonable surrogate measure for insulin resistance have been equivocal[4,10,11]. However, to date there has been only one reported investigation of FIRI for identifying or predicting diseases associated with insulin resistance. Yarnell *et al* used FIRI in the Caerphilly prospective study of ischaemic heart disease, but their results failed to demonstrate relative odds ratios over 1 for either major ischaemic events or all-cause mortality[12]. However, as HDL cholesterol and triglycerides are established biomarkers of insulin resistance, their inclusion in the statistical model with FIRI may represent an overadjustment.

In this communication a comparison of the relative predictive strengths of the selected plasma variables suggested that SHBG was most consistently the strongest biomarker for the three CVD mortalities when unadjusted. Although not consistently the strongest predictor, FIRI was positively related to each of the cardiovascular mortalities selected for analysis; however, only the regression coefficient for myocardial infarction reached significance after adjusting for total cholesterol, BMI, smoking and dietary salt intake. Thus, this communication lends support for the use of FIRI in epidemiological studies, along with other plasma parameters, in potentially identifying disease states associated with the insulin resistance syndrome. The use of FIRI in epidemiological and clinical studies merits broader investigation to assess its usefulness as a biomarker for insulin resistance and related pathologies.

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文摘

胰岛素抵抗综合症(IRS)是指包括高胆固醇血症，糖尿病，高血压和心血管病在内的病症，而这些病症的共同病因是胰岛素抵抗和高胰岛素血症．最近，Duncan等提出用一种称为空腹胰岛素抵抗指数(FIRI)的简单胰岛素抵抗指数于疾病的临床工作和流行病研究．FIRI=空腹血糖空X腹血胰岛素/25．本文探讨了在中国农村进行的一项大规模关于膳食与疾病的生态学研究用FIRI的作用，结果支持这一生物学标志在研究与IRS有关疾病中的应用．

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