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Letters to the Editor

Of insulin resistance and normalcy

Dear Sir,
Ferrannini et al. in their recent paper 'Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome' [1] suggested that Syndrome X variables occurred more frequently in association with each other than expected by chance in a large, mixed Caucasian and Mexican-American population, but their analysis over-represented the relationships.

The Syndrome X features were defined as categorical variables with a prevalence of 54% for obesity and 9–11% for each of impaired glucose tolerance, hypertension, raised triglyceride, raised cholesterol. They reported an association of three or more variables clustering together more often than would be expected by chance alone, and fewer subjects than expected with just two abnormalities.

However, their mathematical analysis did not allow for the expected *absence* of abnormalities, for example the expected paired association of obesity in the hypertension needs to allow for the concomitant absence of associated Type 2 (non-insulin-dependent) diabetes mellitus, impaired glucose tolerance (IGT), raised triglyceride and raised cholesterol. The calculation for the expected paired association is:

Prevalence of obesity with hypertension = prevalence of obesity × prevalence of hypertension × complement Type 2 diabetes ×

Table 1. Recalculation of associations Syndrome X variables in 2930 subjects

		Prevalence of variables %					
		Obesity	Type 2 diabetes	IGT	Hypertensive	Raised triglyceride	Raised cholesterol
Overall prevalence		54.3	9.3	11.1	9.8	10.3	9.2
Complement: no abnormality		45.7	90.7	88.9	90.2	89.7	90.8
Isolated abnormality		29.2	1.3	1.8	1.5	1.0	1.8
Expected isolated abnormality		**31.8**	**3.1**	**3.7**	**2.9**	**3.0**	**2.7**
Prevalence of paired associations							
Type 2 (insulin-dependent) diabetes	O	3.8					
	PE	(5.1)					
	E	**3.7**					
Impaired glucose tolerance	O	4.6					
	PE	(6.0)					
	E	**4.4**					
Hypertension	O	2.2	0.1	0.3			
	PE	(5.3)	(0.9)	(1.1)			
	E	**3.4**	**0.3**	**0.4**			
Raised triglyceride	O	3.0	0.2	0.2	0.1		
	PE	(5.6)	(1.0)	(1.1)	(1.0)		
	E	**3.6**	**0.4**	**0.4**	**0.3**		
Raised cholesterol	O	2.4	0.2	0.1	0.1	0.5	
	PE	(5.0)	(0.9)	(1.0)	(0.9)	(1.0)	
	E	**3.2**	**0.3**	**0.4**	**0.3**	**0.3**	
Prevalence of multiple associations							
% of those with one abnormality		17	40	37	56	51	45
% of the total population		9.2	3.7	4.1	5.5	5.3	4.1
% expected of the total population		4.2	1.5	2.0	2.2	2.3	2.0

O, observed paired association; PE, published expected association e.g. obese, hypertensive 0.543 × 0.098 = 0.053; **E**, expected paired association

complement IGT × complement of raised triglycerides × complement of raised cholesterol.

In addition, since Type 2 diabetes and IGT are mutually exclusive categories, these should be combined to give a prevalence of 20.4 % and complement of 79.6 %. Thus, by reference to Table 1, the expected prevalence of obesity with hypertension is:

$= 0.543 \times 0.098 \times 0.796 \times 0.897 \times 0.908$
$= 0.034$

These data are included in Table 1 and the paired associations appear closer to those expected by chance, although there was still a two-fold greater proportion with multiple associations than expected by chance.

An additional over-estimate of associations between Syndrome X variables arose from their choice of a "normal" control group. It was suggested that subjects with any one abnormal variable were more likely to have abnormalities of other variables. However, the control group was chosen as having *by definition,* no abnormality. Naturally, if this is regarded as 'normal', *by definition* the data for any variable will be greater in any population than in the "normal" population which is a consequence of the definition of the control group rather than a result. This definition of "normal" also leads to an additional potential bias in that their defined "normal" control group contained fewer Mexican-Americans than those who had abnormal variables (mean 57 % vs 71 %, respectively) was younger (39.6 years vs 42.7 years, respectively) and less obese (22.8 vs 29.5 BMI $kg \cdot m^{-2}$, respectively).

The multivariate analyses showed greater differences between the abnormal and control groups for fasting plasma insulin (+ 36 %) and triglyceride (+ 50 %), than for other variables. These trends are probably real, but could have been exaggerated by the use of parametric statistics for variables that are usually log distributed, and multivariate statistics may not have been able to account adequately for differences in obesity between groups.

The authors imply hyperinsulinaemia is a key feature of Syndrome X, but it is not clear whether this was a primary feature or was secondary to variables such as obesity and central obesity. In a similar analysis of newly-diagnosed Caucasian Type 2 diabetic subjects, who were not treated with hypotensive or hypoglycaemic agents, it appeared the majority of associations characterising Syndrome X were secondary to obesity and central obesity rather than being a distinctive identifiable syndrome [2]. Exceptions were significant associations between log triglyceride and log insulin and inversely between log triglyceride and HDL-cholesterol. These could have arisen from specific metabolic defects rather than being part of a global "Syndrome X". This does not imply that variables included in Syndrome X do not have pathological consequences, but it is doubtful (i) whether a specific syndrome exists or (ii) whether obesity/central obesity rather than hyperinsulinaemia are key features in the general population.

Yours sincerely,

R. C. Turner, I. M. Stratton and D. R. Matthews

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Dr. R. C. Turner
Diabetes Research Laboratories
Radcliffe Infirmary
Woodstock Road
Oxford OX2 6HE
UK

Response from the authors

Dear Sir,

Drs. Turner and colleagues make some interesting points. (a) The expected prevalence of paired associations should allow for the expected absence of other abnormalities. Strictly speaking, this is not necessary: one can calculate the expected prevalence of a pair based on the prevalence of the members whether or not other abnormalities are present. In Table 1 of our paper [1], however, we reported the observed prevalence of paired associations in the absence of the other four conditions categorically defined in the analysis. It is therefore more appropriate to compare these observed prevalence rates with the corresponding expected values on equal grounds of exclusion of the other abnormalities. This is what Dr. Turner and his colleagues have done in Table 1 of their Letter. However, that the observed prevalence is lower than expected is still true for 11 of 14 paired associations; this discrepancy also applies to each isolated condition, and the prevalence of multiple associations is invariably higher than expected by roughly two-fold. Thus, the conclusions we drew do not need to be changed at all. Note that we do not attach particular importance to these figures in absolute, as they are obviously influenced by the diagnostic criteria as well as the ethnic composition and constitutional characteristics of the population we sampled [1]. Rather, we emphasise the pattern of overlap of the six conditions examined.

(b) The second point concerns the choice of a "normal" control group, with which we partially disagree. That any variable in a disease group must be different from the control group as a matter of definition is not true for all variables but only for the coding variables. In our analysis, we considered 12 variables, of which only five (BMI, fasting and 2-h plasma glucose, serum total cholesterol and triglycerides) were classification variables. (Hypertension was defined on the basis of antihypertensive treatment rather than measured blood pressure values in 92 % of the cases). Therefore, the differences in the other seven variables between any of the disease groups and the control group were actual results, not consequences of the definition. For example, the presence of statistically significant hyperinsulinaemia, systolic hypertension, and high waist : hip ratio in all disease groups (Table 4 of our paper [1]) is not implicit in the selection of the control group.

Incidentally, in these comparisons multiple regression analysis was employed to account for differences in age, ethnicity, and BMI, as stated in the legend to Tables 4 and 5 of our paper [1]. In addition, in all analyses the values of plasma insulin, glucose, and triglyceride levels were log transformed (this is stated in the Statistical analysis section), although the results were back transformed to calculate the percent differences between the insulin resistant and control groups in Tables 4 and 5 [1]. Thus, on these two latter points Dr. Turner and his colleagues have overlooked our presentation.

But the question, what is the appropriate 'control' for phenotypic characters (eg, plasma insulin concentrations) that have multiple determinants, is more general. Our way of presenting the data of the San Antonio Heart Study in our paper [1] was simply the 'discrete' equivalent of multivariate analysis: we chose categories over continuous variables only to compact and visualise the information.

To exemplify the equivalence of the two approaches, we present in Table 1 the multiple regression equations for fasting and 2-h plasma insulin and serum triglyceride concentrations in the whole database. Multivariate analysis indicates that fasting plasma insulin concentrations are significantly increased in association with obesity, impaired glucose tolerance, Type 2 (non-insulin-dependent) diabetes mellitus, hypertension, and hypertriglyceridaemia independently of one another and after adjustment for age, gender, ethnicity and waist : hip ratio. These results are identical to those obtained with the categorical analysis presented in Table 4 of our paper [1]. In addition, if one calculates from the multiple regression equations in Table 1 the expected mean value of the dependent variables in an ideal "control" subject (ie, a subject with none of the diseases), the following figures result: 54 pmol/l for fasting insulin, 330 pmol/l for 2-h insulin, and 1.2 mmol/l for serum triglycerides (at a mean age of 39.6 years, a mean waist : hip ratio of 0.848, and a 50 % prevalence

Table 1. Multiple regression analysis[a]

	Fasting insulin	2-h insulin	Triglycerides
Constant	1.015 (< 0.000)	3.015 (< 0.000)	3.757 (< 0.000)
Age	− 0.004 (0.009)	− 0.000 (0.845)	0.004 (< 0.000)
Gender	− 0.095 (0.013)	− 0.434 (< 0.000)	0.123 (< 0.000)
Waist/Hip	1.495 (< 0.000)	1.284 (< 0.000)	0.907 (< 0.000)
Ethnicity	0.183 (< 0.000)	0.356 (< 0.000)	0.097 (< 0.000)
Obesity	0.516 (< 0.000)	0.358 (< 0.000)	0.236 (< 0.000)
Type 2 diabetes	0.471 (< 0.000)	− 0.097 (NS)	0.247 (< 0.000)
IGT	0.307 (< 0.000)	0.743 (< 0.000)	0.212 (< 0.000)
HBP	− 0.171 (0.001)	− 0.220 (< 0.000)	− 0.142 (< 0.000)
Hyper Tg	0.234 (< 0.000)	0.206 (< 0.000)	–
Hyper Ch	− 0.023 (NS)	0.107 (0.066)	0.355 (< 0.000)
Multiple R	0.50 (< 0.000)	0.50 (< 0.000)	0.53 (< 0.000)

[a] The values of the dependent variables (fasting and 2-h insulin levels, triglyceride concentrations) are log transformed. Age and waist/hip (ratio) are continuous variables, the others are categorical variables (gender 0 = female, 1 = male; ethnicity 0 = non-hispanic white, 1 = Mexican-American; high blood pressure (HBP) 1 = presence, 2 = absence; Type 2 (non-insulin-dependent) diabetes, obesity, impaired glucose tolerance (IGT), hypertriglyceridaemia (Hyper TG), hypercholesterolaemia (Hyper Ch) 0 = absence, 1 = presence). Diseases defined previously [1]. Numbers in parenthesis are p values. Multiple r = multiple correlation coefficient

of Mexican-Americans). These regression-predicted values are almost identical to the actual mean values for the control group selected by exclusion (Tables 2 and 3 of our paper [1]).

(c) The final point concerns the possibility that we overestimated the prevalence of Syndrome X. The purpose of our analysis was not, however, to prove the existence and gauge the frequency of Syndrome X. We simply showed that, if one takes a pool of individuals in the general population including obese, diabetic, glucose intolerant, hypertensive, and dyslipidaemic subjects, essentially similar metabolic profiles are recovered whichever categorical abnormality is used to enter the pool. One common change (or key feature, as we titled the paper) in the cluster is the presence of hyperinsulinaemia (and, by inference, insulin resistance). We did not mean to imply that hyperinsulinaemia is the causative factor in this insulin resistant pool of individuals. Although, as Dr. Turner and colleagues say, hyperinsulinaemia can have pathological consequences, the analysis of cross-sectional observations cannot provide any evidence that high insulin levels (or any other variable, for that matter) play a causal role in the appearance of the cluster of abnormalities.

As defined by Reaven [2], Syndrome X is the simultaneous presence of diagnostic glucose intolerance, high blood pressure, and dyslipidaemia (high VLDL triglycerides and low HDL cholesterol). By using this definition, the prevalence of Syndrome X in our database is only 0.24% in lean persons, and 1.2% in obese individuals. Fasting plasma insulin levels are 145 and 250 pmol/l, respectively in lean and obese Syndrome X patients, while the corresponding 2-h plasma insulin values are 870 and 1,265 pmol/l. Thus, this Syndrome X is indeed characterised by rather extreme hyperinsulinaemia (Table 3 of our paper [1]) whether it occurs in lean or obese subjects. If, on the other hand, we define the syndrome as the presence of at least one diagnostic abnormality (e.g. diabetes or hypertension), we showed [1] that the syndrome will most often manifest itself with a constellation of clinical and subclinical changes in glucose tolerance, blood pressure, and lipid metabolism. The prevalence of such a primary insulin resistance syndrome can be estimated (in our database) to range between 8 and 10% of the general population when occurring in lean subjects. By including obesity, the prevalence jumps up to 64%. Naturally, one may think, that the insulin resistance syndrome that accompanies obesity is different in origin and significance from that observed in the lean, as Dr. Turner and colleagues infer from their own data in a population of Type 2 diabetic patients [3]. We tend to agree on this, and the final point therefore is that a better understanding is needed of the origin, pathogenetic impact, and prognostic value of reduced insulin sensitivity in non-obese individuals.

Yours sincerely,

E. Ferrannini, S. M. Haffner, B. D. Mitchell and M. P. Stern

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Dr. E. Ferrannini
CNR Institute of Clinical Physiology
c/o Università di Pisa
Via Savi 8
I-56100 Pisa
Italy

Height and glucose tolerance

Dear Sir,

We read with interest the article by Brown and colleagues [1]. In their study, they found that subjects of both sexes with impaired glucose tolerance (IGT) were shorter than matched control subjects with normal glucose tolerance (NGT). The small sumber of patients evaluated (58 IGT subjects) and the lack of similar findings in the literature encouraged us to carry out a similar comparison study in a larger population of patients living at a different latitude.

A total of 163 subjects with IGT (standard 75 g oral glucose tolerance test, National Diabetes Data Group criteria) were compared to NGT control subjects matched for age, sex and waist/hip ratio. We intentionally excluded body mass index as a matching variable since height is actually used to calculate body mass index. Besides anthropometric measures, we also measured plasma lipids (cholesterol and triglycerides) by conventional laboratory methods, serum C-peptide by radioimmunoassay [2] and HbA1c by column chromatography [2]. Comparison of the IGT and NGT groups was made with the unpaired t-test after preliminary analysis of variance (ANOVA).

As shown in Table 1, the male subjects were satisfactorily matched for age, weight and waist/hip ratio. However, we were unable to find any difference between IGT and NGT groups in height, which was almost identical. The IGT patients had significantly higher HbA1c, triglyceride and C-peptide concentrations than the NGT group. Contrary to the male subjects, the IGT females were significantly shorter than control NGT females. As a consequence body mass index was slightly, but significantly ($p < 0.05$) higher in IGT females. As for males, HbA1c, triglycerides and C-peptide levels were significantly higher in the IGT group.

The results can be divided in two discrete parts. As a group, the IGT patients have elevated concentrations of HbA1c and C-peptide: thus, the IGT can significantly affect a reliable index of the overall glucose metabolism and produce augmented insulin secretion from the pancreas in an attempt to overcome insulin resis-