Impaired glucose tolerance

Is it a risk factor for diabetes or a diagnostic ragbag?

The classification of abnormalities of glucose tolerance introduced in 1979 by the National Diabetes Data Group and agreed by the World Health Organisation included the category of impaired glucose tolerance.[1,2] The diagnosis depends on the blood glucose concentration two hours after a glucose load being above normal (6·7 mmol/l) and below the new diabetic value (10 mmol/l). This category satisfied a need for defining a level of glucose intolerance that was not clearly normal but that was also not sufficiently severe to predict microvascular disease, particularly retinopathy, in prospective studies.

As a group, people with impaired glucose tolerance have raised concentrations of insulin both when fasting and after a glucose load[3-5] and show insulin resistance when investigated with glucose clamp techniques.[4,6] Several studies of the natural course in people with impaired glucose tolerance have shown that they are at increased risk of developing diabetes (table I),[7-21] but there is less consensus about the excess risk of cardiovascular disease.[22-27] Recently Saad *et al* reported an extremely high incidence of non-insulin dependent diabetes in Pima Indians with impaired glucose tolerance,[19] the rate of deterioration to diabetes of 5-6% a year over 10 years exceeding the rates of 1·5-4% reported in most studies in other populations.[10-12,15-17] In a separate paper the same authors show that even "transient" impaired glucose tolerance is associated with an increased risk of "deterioration to diabetes."[20] Other recent studies have, however, cast doubt on the concept of impaired glucose tolerance, both because of its ephemeral nature (table II)[28-30] and as a consequence of doubts about whether it warrants categorisation as a separate entity.[31]

Stern *et al* analysed the concept of impaired glucose tolerance, suggesting that the category represented a heterogeneous group of people.[32] They used the model of a population with a bimodal distribution of two hour blood glucose concentrations to propose that the category of impaired glucose tolerance will contain some people in the upper tail of normal glucose tolerance ("impaired glucose tolerance normals"), some in the lower tail of diabetic patients ("false negative diabetics"), and some who are truly in the impaired glucose tolerance category. If the distribution of two hour blood glucose concentration is bimodal Stern *et al* suggested that for the nadir to remain apparent few people must have true impaired glucose tolerance, and, therefore, the rate of deterioration through the impaired glucose tolerance category must be fairly rapid. For this reason they defined the third category as "impaired glucose tolerance in transition." Although their model is derived from an analysis of the overlap of two modes of a bimodal population, we believe that it may be more widely applicable and that both the intraindividual variance of the test and the interindividual differences in the population may contribute to blurring the classification. In this article we analyse the concept of deterioration to diabetes and the instability of the impaired glucose tolerance class in the light of data on the variability of the biological response to a glucose load. We conclude that additional criteria are required to categorise people with impaired glucose tolerance and that measures of insulin and of proinsulin like molecules are possible candidates for this task.

Variability of the glucose tolerance test

Early observations on the variability of the blood glucose response to a glucose load found coefficients of variation of between 20% and 35% in the two hour blood glucose concentration with little evidence of differences in these values (when expressed in percentage terms) in the different glucose tolerance classes.[30,33-39] In one study in a predominantly white population we investigated glucose tolerance in response to a 75 g load in 223 subjects on two occasions less than one year apart and found a coefficient of variation for the two hour blood glucose concentration of 32·5% with no evidence of any difference in this variability with different degrees of glucose intolerance.[30] There was evidence of regression to the mean in that more subjects with impaired glucose tolerance were reclassified to normal than were reclassified as diabetic, but there was no difference in mean blood glucose concentrations in the population as a whole between the two tests.

The implication of the biological variability of the glucose tolerance test is likely to be much smaller for people classified as normal or diabetic than for those categorised as having impaired glucose tolerance. Because the impaired glucose tolerance category has a range of two hour blood glucose concentration of only 3·3 mmol/l the two margins are only 0·5 SD away from the midpoint. Thus if a population is selected as having impaired glucose tolerance on the basis of a single test result only a small proportion would be expected still to have impaired glucose tolerance on repeat testing—whether the test is repeated at one week or five years. In three published and two unpublished studies in which glucose tolerance tests were repeated in people with impaired glucose tolerance after an interval of less than one year the rate of reversion to normal tolerance was 28-67% and that of "deterioration to diabetes" 4-9% (table II).[28-30]

The fact that people discovered to have impaired glucose tolerance in the first test are reclassified on repeat testing begs the question where they really belong. Someone with a two hour blood glucose concentration of 9·5 mmol/l in the first test and of 6·5 mmol/l in the second could be in the category of "impaired glucose tolerance normal" and returning to the biological set point or in the category of "impaired glucose tolerance in transition" and testing low on the day of the second test. We have looked at electrocardiographic evidence of coronary heart disease in 52 people classified as having impaired glucose tolerance on the basis of the results of a single glucose tolerance test and found that the prevalence of these changes increases with increasing degrees of intolerance on the second test.[40] This supports the hypothesis that these 52 people comprised a mixture of "impaired glucose tolerance normals" with a low prevalence of coronary heart disease, "false negative diabetics" with a higher prevalence of coronary heart disease, and some patients with true impaired glucose tolerance, perhaps in transition.

TABLE I—*Progression to diabetes mellitus in people with impaired glucose tolerance according to various studies*

Authors	Subjects studied	Mean or range of age (years)	No of subjects rescreened	Time between initial and second or final glucose tolerance test (years)	Criteria for impaired glucose tolerance	Glucose load (g)	Diagnostic criteria for diabetes	Results of second or final glucose tolerance test: Normal glucose tolerance (%)	Impaired glucose tolerance (%)	Diabetes (%)	Unclassified (%)	Average rate of development of diabetes per year	Cumulative incidence (%): Five years	Cumulative incidence (%): Ten years	Comments
O'Sullivan and Mahan, 1968[7]	Non-pregnant ambulant American women	19-50	352	1-12	Three sets of criteria (2 h blood glucose >5·6-6·7 mmol/l)	100	Clinical decompensation			10-26		2·1-5·2	21	52	Risk of deterioration dependent on criteria for glucose intolerance
Köbberling *et al*, 1975[8]	First degree relatives of diabetic patients	56	118	5	Fasting blood glucose <6·7 mmol/l but 1 h blood glucose plus 2 h blood glucose >16·7 mmol/l	75	Second glucose tolerance test	36	51	14		2·8			
Birmingham study, 1976[9]	Citizens of Birmingham	Adults	31	10	2 h Blood glucose >7·5 mmol/l	50	Second glucose tolerance test	32	23	45		4·5			Subjects screened were positive for glycosuria
Sartor *et al*, 1980[11]	Swedish men	52	206	10	3 h Glucose tolerance test; any of 10 blood glucose concentrations >2 SD <3 SD above mean	30 g/m²	Fasting blood glucose >7·8 mmol/l on more than one occasion			17 (Overall incidence)		1·7		17	Proportion deteriorating to diabetes: 29% of those untreated, 15% of those treated by diet, 0% of those treated by diet plus tolbutamide
Keen *et al*, 1982[12]	Citizens of Bedford, England	56	241	10	2 h Blood glucose 6·7-11·1 mmol/l	50	Results of about 17 follow up blood glucose tests, usually after 50 g glucose load*	53	23	15	9	1·5	9	15	Treatment with tolbutamide did not alter natural course of impaired glucose tolerance
Sasaki *et al*, 1982[13]	Citizens of Osaka, Japan	57	13	7	WHO	50	Second glucose tolerance test	39	23	39		5·6			Rescreened 207 of 507 subjects
Ito *et al*, 1983[14]	Citizens of Hiroshima, Japan	25-86 (Most were in their 60s)	171	5-17	NDDG	50/75	Annual glucose tolerance test	13	20	47	20	6·6			All subjects had glycosuria on initial testing
King *et al*, 1984[15]	Micronesians in Nauru	38	51	6·2	WHO	75	Second glucose tolerance test	39	35	26		4·0			Incidence/% per annum in those with normal glucose tolerance
Kadowaki *et al*, 1984[16]	Japanese outpatients attending adult diseases clinic	49	288	8·7 (5-12)	2 h Blood glucose 7·2-13·3 mmol/l	100	Fasting blood glucose once every four months, one value >7·8 mmol/l or >6·7 mmol/l with retinopathy			17		2·0			
Jarrett *et al*, 1984[17]	Male civil servants in London	56	204	10	Several including 2 h blood glucose 6·7-11·0 mmol/l	50	Results of about 16 follow up blood glucose tests, usually after 50 g glucose load†			29		2·9	16	29	Treatment with phenformin or diet did not alter natural course of impaired glucose tolerance
Ramachandran *et al*[18]	Indians	35-72	107	4·3 (2-10)	NDDG	75	Second glucose tolerance test	32	32	36		8·4			
Saad *et al*, 1988[19,20]	Pima Indians	32	384	Median 3·3 (1·6-11·5)	WHO	75	Repeated glucose tolerance tests every two years	43	26	31		6·1	25	61	Final test performed in 384 of 566 subjects with impaired glucose tolerance
Motala *et al*‡	Asian Indians in South Africa		29	2	WHO	75	Second glucose tolerance test	28	45	28		14			
Schranz, 1989[21]	Maltese	35-74	75	6	WHO	75	Second glucose tolerance test	33	36	31		5·1			

*Two consecutive or three non-consecutive two hour blood glucose concentrations >11·1 mmol/l or raised blood glucose concentration with symptoms or two hour blood glucose concentration >11·1 mmol/l in last glucose tolerance test.
†Two consecutive or three non-consecutive two hour blood glucose concentrations >11·1 mmol/l or raised blood glucose concentration with symptoms or two hour blood glucose concentration >11·1 mmol/l in glucose tolerance test at five to 10 years.
‡A A Molata *et al*. Paper presented to the thirteenth International Diabetes Federation satellite congress, Hobart, Tasmania, 1988.
WHO=World Health Organisation.
NDDG=National Diabetes Data Group.

TABLE II—*Instability of glucose tolerance classification in subjects with impaired glucose tolerance on repeat testing within one year*

Authors	Subjects studied	Mean or range of age (years)	No of subjects rescreened	Time between initial and second glucose tolerance test	Criteria for impaired glucose tolerance	Glucose load (g)	Results of second or final glucose tolerance test: Normal glucose tolerance (%)	Impaired glucose tolerance (%)	Diabetes (%)	Unclassified (%)
Riccardi *et al*, 1985[28]	Employees of an Italian telephone company	40-59	67	2-4 months	EASD	75	35	56	9	
Glatthaar *et al*, 1985[29]	Australian citizens	≥25	115	2-5 months	WHO	75	48	37	16	
Forrest *et al*, 1988[30]	Londoners	≥40	35	8·5 (0·5-12) months	WHO	75	28	51	9	11
Tuomilehto *et al**	Finnish citizens	45-64	286	2-3 months	WHO	75	67	23	4	
Swai *et al*†	Rural Tanzanians	≥15	224	<7 days	WHO	75	76	21	3	

*J Tuomilehto *et al*. Paper presented to the thirteenth International Diabetes Federation satellite congress, Hobart, Tasmania, 1988.
†A B M Swai *et al*. Paper presented to the thirteenth International Diabetes Federation satellite congress, Hobart, Tasmania, 1988.
WHO=World Health Organisation. EASD=European Association for the Study of Diabetes.

There is some recent evidence of another factor that may contribute to the changing of category among people shown by a single test to have impaired glucose tolerance. We recently performed a study in six villages in rural Tanzania in which a 75 g glucose load was given to 6299 people (paper presented to the 13th International Diabetes Federation satellite congress, Hobart, Tasmania, 1988). In some 8% of these a repeat glucose tolerance test was performed within seven days. On the second occasion only one quarter of the people with a two hour blood glucose concentration exceeding 10·0 mmol/l on first testing were still "diabetic," while over three quarters of those with initial impaired glucose tolerance had reverted to normal and 3% had diabetes. That this was not simply regression to the mean was shown by the fact that when the population levels of two hour blood glucose concentration were reconstructed from this stratified sample there was a highly significant decrease of 0·4 mmol/l between values at screening and those at recall and the estimated population prevalence of impaired glucose tolerance fell from 7·6% to 3·3% on repeat testing.

Thus rather than merely showing glucose tolerance test variability and regression to the mean this population seemed to show a stress effect on glucose tolerance, implying that two hour blood glucose concentrations may respond to investigation with a similar "arousal," or "defence," reaction to that often described for blood pressure.[41-43] It is not clear whether the degree of "settling" of values of two hour blood glucose concentration in these people correlated with other evidence of a lesser degree of arousal on the day of the second test. Nor is it known whether this phenomenon occurs widely rather than being a feature of arousal or anxiety in a population that is not routinely exposed to medical investigation. If the phenomenon is widespread it would imply that the epidemiological survey of glucose intolerance in a population may appreciably overestimate the prevalence of both impaired glucose tolerance and diabetes.

At first glance assays of glycated haemoglobin or glycated protein might offer potential advantages in classifying disorders of glucose tolerance, their biological variability and dependence on nutritional state being far lower than those for blood glucose concentrations.[44] These benefits must, however, be set against the narrower biological range for these variables. Glycated haemoglobin concentrations are not raised in people defined as having impaired glucose tolerance in the glucose tolerance test.[45 46] In preliminary studies we have found that the values of two hour blood glucose concentrations are better able to discriminate the presence of vascular disease in a diabetes screening study than the results of any of four assays of glycated haemoglobin.[47]

What is "deterioration to diabetes?"

There are, then, many problems in defining a true change in glucose tolerance category, particularly in people with impaired glucose tolerance. If the variability of a test can result in the recategorisation of people as "deteriorating to diabetes" and thereby exclude them from further study the frequency of such "deterioration" will be substantially overestimated. To show a true change in a variable that has a poor biological or assay reproducibility the change in the level of the variable should exceed 2 SD of the intraindividual variation. This criterion will, however, merely define 2·5% of the population as having deteriorated in the second test. The method employed in the Bedford and Whitehall surveys to define deterioration to diabetes was the requirement for two consecutive or three non-consecutive two hour *capillary* blood glucose values (after a 50 g oral glucose load) to be equal to or more than 11·1 mmol/l (or symptoms and signs of hyperglycaemia).[10 12 17] Because the glucose tolerance test used to define impaired glucose tolerance was performed only once, however, those so defined might include people with impaired glucose tolerance who were "false negative diabetics" re-establishing their biological set point. A more satisfactory approach would be to repeat the glucose tolerance test on at least three occasions each time in order to reduce the coefficient of variation to less than 20%, but this is unacceptably demanding for both subjects and investigators.

The value of the study in Pima Indians is that knowledge of the previous degree of glucose tolerance in people with impaired glucose tolerance allows exclusion of these "false negative" diabetics from investigation.[19] Nevertheless, the high rate of deterioration to diabetes of these people was probably found because only one two hour blood glucose concentration of 11·1 mmol/l or more was necessary to define diabetes, and this may have occurred frequently in people with true set impaired glucose tolerance or even, on occasions, in those with concentrations at the upper end of the normal range. The observation that rates of "deterioration to diabetes" increase when criteria are less rigorous was noted in the Whitehall study.[10 17]

Several studies have looked at factors that may improve the ability to predict deterioration to diabetes in people with impaired glucose tolerance. In Pima Indians,[19] as well as in Japanese[16] and Nauruans,[48] a poor insulin response to a glucose load predicts deterioration. Nevertheless, cross sectional studies of glucose intolerance may misclassify diabetic patients as having impaired glucose tolerance, and these patients may show an impaired insulin response to a glucose load as a consequence of diabetes.[4 49 50] If a later glucose tolerance test were to show deterioration to diabetes in these people the poor insulin response might falsely be interpreted as a predictor, rather than a consequence, of diabetes. The Pima Indian study is unique as the longitudinal data make it improbable that those with impaired glucose tolerance were false negative diabetics. The ability, shown in other studies, of using either fasting or two hour plasma glucose concentrations to predict deterioration to diabetes[12 14-17 19 48] could again reflect the possibility of an initial false negative glucose tolerance test result.

Is bimodality a common phenomenon?

We suggest (as do Stern *et al*[32]) that the data need reinterpreting to define better glucose tolerance in populations, employing continuous and not categoric variables and using dynamic rather than static analyses. The bimodal distribution of blood glucose concentrations may be much more widely distributed than in isolated populations[51–55] but inapparent for four reasons.

(1) The second mode may be reduced by treating known diabetic patients.

(2) The prevalence of diabetes may be too low to show the second mode. Rushforth *et al* estimated that a prevalence of at least 10% was necessary to see bimodal distribution,[51] though it has been found in a population with a prevalence of diabetes of 6·7%.[53]

(3) The second mode may be less homogeneous in most populations than in the populations for which bimodality has been described. In three of these four populations there was a remarkable consistency of the mean (SD) of the second mode at around 19 (5) mmol/l.[51 52 54] Furthermore, when expressed as a coefficient of variation the value was no greater than would be expected from the intraindividual variation of the glucose tolerance test alone, suggesting that interindividual variation contributes very little to the observed population variance. Probably, however, in a more heterogeneous population—in which both insulin deficiency and resistance may contribute to the aetiology of non-insulin dependent diabetes[56]—there would be a much greater interindividual variance within the diabetic mode. For a population of diabetic patients with values for the mean and standard deviation of two hour blood glucose concentration of the three bimodal populations considered above, the number of false

TABLE III—*Crude prevalence of impaired glucose tolerance and diabetes in different populations*

Authors	Subjects studied	Mean or range of age (years)	No of subjects	Criteria for impaired glucose tolerance	Subgroup	Results: Impaired glucose tolerance (%)	Results: Diabetes mellitus (%)
Zimmet *et al*, 1983[61] and Coventry *et al*, 1986[67]	Residents of Fiji	39	2638	WHO	Rural Melanesian:		
					Men	6·2	1·7
					Women	10·2	1·7
					Urban Melanesian:		
					Men	8·0	4·8
					Women	13·8	8·2
					Rural Indian:		
					Men	10·4	12·7
					Women	10·8	12·9
					Urban Indian:		
					Men	9·4	14·1
					Women	11·2	12·3
Zimmet *et al*, 1984[62]	Micronesians in Nauru	36	1546	WHO	Men	18·4	24·6
					Women	18·3	23·9
King *et al*, 1984[63]	Highland villagers in Papua New Guinea	≥20	308	WHO	Men	3·5	
					Women	1·2	
King *et al*, 1984[64]	Micronesians in Kiribati	≥20	2911	WHO	Rural:		
					Men	12·5	3·6
					Women	14·3	3·6
					Urban:		
					Men	15·0	8·1
					Women	16·9	7·4
Verrillo *et al*, 1985[65]	Rural Italians	18-92	1154	WHO	Men	4·9	7·0
					Women	7·7	6·9
Glatthaar *et al*, 1985[29]	Australian non-aborigines	≥25	3197	WHO	Men	4·3	5·1
					Women	3·3	3·7
Tuomilehto *et al*, 1986[66]	Finnish men	65-84	688	WHO	East Finland	31·6	29·7
					West Finland	32·0	29·9
Forrest *et al*, 1986[68]	Londoners	>40	1040	WHO		4·1	4·6
Harris *et al*, 1987[69] and Harris *et al*, 1989[72]	Citizens of the United States	20-74	3872	WHO	White:		
					Men	10·2	5·5
					Women	11·1	7·3
					Black:		
					Men	11·3	8·6
					Women	13·6	11·0
					Age (years):		
					20-44	6·4	2·0
					45-54	14·8	8·5
					55-64	15·1	13·4
					65-74	22·8	18·7
Fujimoto *et al*, 1987[70]	Japanese Nisei men in the United States who self reported as non-diabetic	61	153	WHO		39·2	11·1
						36 (estimated population prevalence)	20
Modan, 1988*	Israelis	40-69	2299	NDDG	Age (years):		
					40-49	17·7	7·1
					50-59	22·5	17·4
					60-69	27·3	33·0
O'Dea *et al*, 1988[71]	Australian aborigines in the north western desert	35	148	WHO	Age (years):		
					<35	16·4	1·3
					≥35	34·8	14·5
McLarty *et al*, 1989[73]	Rural Tanzania	≥15	6083	WHO	Age (years):		
					<45	5·5	0·4
					≥45	12·5	1·9
King *et al*, 1989[74]	Village in Papua New Guinea	≥20	799	WHO	Rural		0·7
					Periurban coastal	0·7	4·0
					Periurban highland	1·9	

*M Modan. Paper presented to the thirteenth International Diabetes Federation satellite congress, Hobart, Tasmania, 1988.
WHO=World Health Organisation.
NDDG=National Diabetes Data Group.

negative diabetics in the impaired glucose tolerance category would be only 2·5% of the number of the diabetics, whereas in a diabetic population with a greater range of two hour blood glucose concentration, or a lower second mode mean value, this proportion may be substantially greater, so blurring the nadir between the modes.

(4) The nadir between the modes may contain many people with impaired glucose tolerance who are slowly in transition to diabetes. The rate of deterioration from normal to diabetic tolerance has not been studied other than in Pima Indians, a population in which the prevalence of diabetes increases rapidly in the third and fourth decades.[57] Similar analysis of chronological changes in two hour blood concentrations in people of other populations originally having normal test results and then having impaired glucose tolerance on retesting should allow the rate of deterioration to be calculated as a best fit slope on a regression line, so that the average rate of transition could be expressed in a similar way to that employed by renal physicians, with reciprocal creatinine concentrations or glomerular filtration rate. This would permit the natural course of impaired glucose tolerance to be compared in different populations and thereby facilitate the investigation of the possibility of bimodality in other populations.

Stern *et al* have suggested that in the populations displaying bimodality the nadir between the two modes may be higher than 11·1 mmol/l, the two hour blood glucose concentration used to define diabetes mellitus.[55] Whether this is also the case for the threshold for microangiopathy is not clear. This would still be compatible with the finding of retinopathy at follow up of patients found to have diabetes mellitus with two hour blood concentrations of 11-13 mmol/l if these patients had had a low result in the screening test or had since deteriorated.[58-60] Any studies intended to clarify such characteristics of glucose tolerance and their relation with complications would require many more reproducible data on the individual patient than currently exist.

There is a wide variation in the ratio of the prevalence of non-insulin dependent diabetes to the prevalence of impaired glucose tolerance in different societies[29 61-74] and, as impaired glucose tolerance is more weakly related to age than is diabetes mellitus, even in people of different ages within the same population (table III).[61-63 65 69 71-73] This may be because some populations (such as those with a high prevalence of impaired glucose tolerance compared with the prevalence of diabetes) have a skewed unimodal distribution and others (with a higher prevalence of diabetes) a bimodal one; the diabetic two hour blood glucose concentration mode differs in different populations; the degree of skew of a single curve differs; or the number of people with impaired glucose tolerance or its rate of transition differs. With data on rates of transition and by using continuous rather than categoric variables these analyses should also be possible.

Conclusions

The category of impaired glucose tolerance is heterogeneous because of both the distribution of patterns of glucose intolerance in populations and the variability of the test employed to characterise glucose intolerance in individual people. It is clearly impracticable to repeat a glucose tolerance test several times to define the severity of glucose intolerance, so other methods are necessary to distinguish the three subgroups of impaired glucose tolerance.

People with impaired glucose tolerance show hyperinsulinaemia and insulin resistance, both in cross sectional[4 6] and in longitudinal[5] studies. As a group their mean concentrations of insulin when fasting and two hours after a glucose load are increased by roughly 50% and 250% respectively,[4 5] while their insulin stimulated glucose disposal is reduced by some 70%.[6] Though a true deterioration from normal to impaired glucose tolerance is associated with an increase in fasting and post-load insulin concentrations and in insulin resistance, it is not clear whether a person classified as "impaired glucose tolerance normal" would also show hyperinsulinaemia during the abnormal glucose tolerance test. Possibly, therefore, measures of insulin, employed as surrogates for those of insulin resistance, might help define patients with true impaired glucose tolerance.[5 6]

Not all people with impaired glucose tolerance progress to diabetes; those who do seem to show a deterioration in insulin response to glucose, suggesting that insulin deficiency, superimposed on insulin resistance, is the cause of the further deterioration in glucose tolerance.[5] If this is so measures of insulin might distinguish two subgroups of patients with true impaired glucose tolerance: those in transition (who deteriorate to diabetes) showing failing β cell function and those with persistent hyperinsulinaemia who remain glucose intolerant.

Hyperinsulinaemia in the presence of raised fasting concentrations of glucose is taken to imply insulin resistance.[56] Though insulin resistance has been shown in people with impaired glucose tolerance and diabetes by using infusions of exogenous insulin,[6] "hyperinsulinaemia" in diabetic patients may be in part a manifestation of raised concentrations of intact and split proinsulin,[75] which seem to be detected by standard radioimmunoassays for insulin.[76] The implication of these findings is that insulin deficiency may be a more important contributor to the aetiology of diabetes than has been suspected, but it remains to be seen whether "impaired glucose tolerance normals" and "false negative diabetics" might be distinguished from patients with true impaired glucose tolerance by the use of more sensitive and specific assays for insulin-like molecules. Preliminary findings have suggested that raised concentrations of these molecules—rather than of insulin per se—are associated with the excess cardiovascular risk in diabetic patients,[77] and it is an intriguing possibility that both the hyperinsulinaemia and the cardiovascular risk associated with impaired glucose tolerance may also represent the consequences of raised concentrations of these molecules.

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