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ORIGINAL ARTICLE

Relationships between glycaemic abnormalities, obesity and insulin resistance in nondiabetic Polynesians of New Caledonia

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Objective: Polynesians in New Caledonia have an increased risk for developing diabetes, compared to Melanesians or Europeans. They are also more prone to obesity. The aim of this study was to analyse differences in the pre-diabetic state that may explain the varying susceptibility to diabetes between these three ethnic groups, focusing on the balance between insulin resistance and capacity of pancreatic cells to secrete insulin.
Design and subjects: The CALDIA Study is a population-based cross-sectional survey of diabetes prevalence conducted in New Caledonia. All participants who did not have diabetes, according to the results of a 0–2 h oral glucose tolerance test ($n = 392$), were selected for analysis.
Results: Compared to Europeans, Polynesians and Melanesians had significantly higher body mass indices (BMI) and waist-to-hip ratios (WHRs). Polynesians had higher fasting plasma glucose values than Europeans or Melanesians (6.03 mmol/l, vs 5.78 and 5.46, respectively; $P < 0.0001$). Fasting plasma insulin level and the estimate of insulin resistance by homeostasis model assessment were not significantly different between the three ethnic groups. Homeostasis model assessment estimate of β-cell secretory capacity was lower in Polynesians compared to the two other ethnic groups (83.1 mU/mmol, vs 119.3 and 125.2, respectively; $P < 0.02$).
Conclusion: Despite a high prevalence of central obesity, as judged by high BMI and WHR, in Polynesians of New Caledonia, their high risk of diabetes may be more strongly related to a defect in insulin secretion capacity than to insulin resistance.
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Introduction

Type 2 diabetes is considered to be the result of a two-step process.[1] In the first 'prediabetic' step characterized by insulin resistance, compensatory hyperinsulinaemia helps maintain normal glucose levels. In the second step, there is a decline in β-cell secretory capacity together with a progressive elevation of glucose levels that define diabetes.[2] This two-step mechanism has been shown to apply to many populations around the world (e.g. Pima Indians, Micronesians, Mexican Americans, South Asians).[3] However, the balance between insulin resistance and deficient insulin secretion in the pathogenesis of type 2 diabetes appears to vary between ethnic groups.[4] Regarding Polynesians, a population with a high prevalence of obesity and diabetes, one study in New Zealand reported that, after adjustment for body mass index (BMI), Polynesians were not more insulin-resistant than Europeans, who are much less susceptible to diabetes.[5]

Previous publications from the CALDIA Study, a large diabetes screening survey conducted in the multiethnic population of New Caledonia, have shown that Polynesians indeed had the highest degree of central obesity, and the highest prevalence rate of diabetes compared to the other two major ethnic groups living in the archipelago (15.3 vs 8.4% in Melanesians or Europeans).[6,7] In order to further examine the abnormalities that could explain their higher risk of diabetes, we selected from the CALDIA database nondiabetic subjects with the purpose of comparing the degree of insulin resistance and of β-cell secretory capacity (using the homeostasis model assessment, or HOMA) between ethnic groups.

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Population and methods

The CALDIA Study was conducted from 1992 to 1994 to determine the prevalence of diabetes in New Caledonia. The rationale, design and methods of the study were previously described in detail.[6] To summarize, the target population for the CALDIA Study were subjects aged 30–59 years, resident in New Caledonia for more than 10 years. Subjects were recruited all over the territory (North province, Noumea and Loyalty Islands). In the North province, 12 small towns and 101 villages out of 199 were randomly selected. In Noumea, six suburbs were chosen because they included all the ethnic groups. In the Loyalty Islands, all 85 villages participated. As a whole, 9390 subjects (representing a response rate of 78%) were visited at home for screening, where they all had a capillary blood glucose (CBG) measurement with a reflectance meter (One Touch®, LifeScan, Johnson & Johnson, Milpitas, CA, USA). All previously known diabetic subjects and subjects having a CBG value $\geqslant 6.1$ mmol/l when fasting, or CBG $\geqslant 7.8$ mmol/l when nonfasting ($n = 643$), were invited to come to the health centre for a more detailed examination. The response rate for this examination was 91.5% (588 subjects). At the same time, a selection of 517 subjects with CBG < 6.1 mmol/l, matched by ethnic group, gender, age and location, also underwent the examination.

At the health centre, participants answered a standardized questionnaire and underwent anthropometric measurements. BMI (weight (kg)/height $(m)^2$) was used to report general obesity. According to the World Health Organization (WHO) criteria,[8] subjects with BMI 25–29.9 Kg/m^2 were considered overweight and subjects with BMI $\geqslant 30$ Kg/m^2 were classified as obese. Waist and hip circumferences were measured in the standing position to the nearest centimetre, the first at the umbilicus and the second at the iliac crest. The waist-to-hip ratio (WHR) was calculated as an index of upper-body adiposity.

A 2-hour oral glucose tolerance test (OGTT) with a 75-g glucose load was performed according to the WHO recommendations.[9] Blood samples were locally centrifuged, frozen and sent to Noumea central laboratory. Fasting plasma glucose (FPG) and 2-h plasma glucose (2h-PG) levels were assessed by the glucose oxidase method in Noumea. Fasting plasma insulin (FPI) was measured by radioimmunoassay (RIAgnost, Behring, Los Angeles, CA, USA) at the Henri Mondor Hospital, Créteil, France.

The study protocol and procedures were approved by all local medical commissions involved, and all participants gave informed consent for their participation.

Among the 1105 subjects having a complete examination, we excluded diabetic subjects, known or newly diagnosed, that is those with FPG $\geqslant 7$ mmol/l or 2h-PG $\geqslant 11.1$ mmol/l at the OGTT.[9] One unclassified subject was also excluded. Of the remaining subjects, only those of European, Melanesian or Polynesian origin were retained. Subjects were classified as normoglycaemic (FPG < 6.1 mmol/l and 2h-PG < 7.8 mmol/l), having impaired fasting glucose (IFG) (6.1 mmol/l $\leqslant$FPG < 7.0 mmol/l and 2h-PG < 7.8 mmol/l), or impaired glucose tolerance (IGT) (7.8 mmol/l $\leqslant$2h-PG < 11.1 mmol/l, irrespective of FPG values).[9] To assess insulin resistance and β-cell function, the HOMA[10] was applied to fasting plasma glucose and insulin values as follows: insulin resistance (HOMA-IR) = FPI (mU/l) $\times$ FPG (mmol/l)/22.5; β-cell function (HOMA-BC) = [20 $\times$ FPI (mU/l)]/[FPG (mmol/l)-3.5].

Age, sex, anthropometric variables and variables characterising glucose-insulin regulation were compared between the three ethnic groups using χ^2 test for categorical variables and analysis of variance for continuous variables. Glucose homeostasis variables were also compared after multiple adjustment for age, sex and BMI, by analysis of covariance. When comparisons were statistically significant, two-by-two comparisons were carried out, using the Bonferroni correction. Continuous variables with a log-normal distribution were log-transformed before testing, and back-transformed into natural values for presentation. All statistical analyses were performed with SAS statistical package software version 9.1 (SAS Institute, Cary, NC, USA).

Results

After exclusion of subjects with missing values for the variables of interest, analysis was performed on 392 subjects (57 Europeans, 287 Melanesians, 48 Polynesians). Their general characteristics are shown in Table 1. Age and sex distribution were not significantly different between the groups. Mean BMI and WHR were highest in Polynesians and lowest in Europeans. Overweight and obesity were significantly more prevalent ($P < 0.0001$) in Polynesians or Melanesians than in Europeans.

Nonadjusted and age, sex and BMI-adjusted comparisons of variables characterising glucose-insulin regulation are shown in Table 2. Fasting plasma glucose values were significantly different between the three groups, with the highest mean value observed in Polynesians, who also had the highest prevalence rate of glycaemic anomalies (IFG or IGT: 43.7 vs 35.1% in Europeans and 22.6% in Melanesians, $P < 0.01$). Non-adjusted 2-h plasma glucose was not significantly different between the three groups, but the differences became significant when adjusted for age, sex and BMI. Despite the marked differences in morphotype between the groups, the geometric means of fasting insulin and HOMA-IR were not significantly different. By contrast, there was a significant difference ($P < 0.02$) for the marker of insulin secretion capacity, HOMA-BC, with the lowest value observed in Polynesians. When the analysis was performed after adjustment for BMI, the differences became significant for FPI ($P < 0.004$) and HOMA-IR ($P < 0.002$). The two-by-two comparisons with Bonferroni adjustment (Table 3) indicated that for these markers of insulin resistance, the differences were between Europeans and the two other ethnic groups, with Europeans having significantly higher indices of insulin resistance. By contrast, insulin secretory capacity was

significantly lower in Polynesians compared to the two other ethnic groups.

To better understand this finding, the three ethnic groups were divided according to BMI (normal, overweight or obese). At any given body mass, Polynesians had the highest fasting glucose values together with the lowest fasting insulin values, denoting a clear lack of insulin, both absolute and relative to glucose values (Figure 1, panels a and b). This was confirmed by the fact that the curve for HOMA-BC in Polynesians was consistently and largely lower, at any given body mass, compared to the two other groups (Figure 1, panel c).

Discussion

Polynesians are known to be a population at high risk for type 2 diabetes. This was confirmed in the CALDIA Study, where diabetes prevalence rate was twice that observed in Europeans or Melanesians.[6] Moreover, in our analysis restricted to nondiabetic subjects, Polynesians were markedly overweight with upper-body obesity, and they already exhibited abnormalities of glucose homeostasis (higher FPG values and lower prevalence of normoglycaemic subjects), which are signs of susceptibility to diabetes.[11] Although obesity is commonly associated with insulin resistance and hyperinsulinaemia, and the classical view is that these anomalies are markers of the prediabetic state,[12–14] the only accompanying anomaly we found in Polynesians was a relative defect in insulin secretion. The fact that our radioimmunoassay was not specific for insulin does not challenge the finding, as, if there are differences of proinsulin proportion between the study groups, it is probably higher in Polynesians given their 'worse' glucose homeostasis. After adjustment for BMI, insulin sensitivity in both Polynesians and Melanesians was actually greater than in Europeans. Although we used an indirect method (HOMA) for

Table 1 General characteristics of the participants, by ethnic group

	Ethnic group			P
	Europeans n = *57*	*Melanesians* n = *287*	*Polynesians* n = *48*	
Age (years)	47.1 (45.2–49.0)	47.0 (46.1–47.8)	47.9 (45.6–50.1)	NS
Men	23 (40.4)	96 (33.5)	16 (33.3)	NS
BMI (kg/m²)				
<25	27 (47.4)	57 (19.9)	13 (27.1)	<0.0001
25–29	22 (38.6)	120 (41.8)	15 (31.2)	
⩾30	8 (14.0)	110 (38.3)	20 (41.7)	
Mean[a]	25.5 (24.6–26.5)	28.7 (28.1–29.2)	29.0 (27.2–31.0)	<0.0001
WHR	0.89 (0.86–0.91)	0.92 (0.91–0.93)	0.94 (0.92–0.96)	<0.001

Values are means (95% confidence intervals) for continuous variables, or numbers (percentages) for categorical variables. Abbreviations: BMI, body mass index, WHR, waist-to-hip ratio. [a]Log-transform applied.

Table 3 Two-by-two comparisons between the ethnic groups for markers of glucose-insulin regulation

	Ethnic group		
	Europeans vs Melanesians	*Europeans vs Polynesians*	*Melanesians vs Polynesians*
FPG	<0.0003	NS	<0.0001
2h-PG	<0.05	NS	NS
FPI	<0.007	<0.007	NS
HOMA-IR	<0.001	<0.02	NS
HOMA-BC	NS	<0.004	<0.003

Abbreviation: FPG, fasting plasma glucose, FPI, fasting plasma insulin, HOMA-BC, homeostasis model assessment β-cell secretory capacity, HOMA-IR, homeostasis model assessment of insulin resistance, 2h-PG, 2 h-plasma glucose, NS, not significant. Levels of significance are corrected using the method of Bonferroni.

Table 2 Markers of glucose-insulin regulation by ethnic group

	Ethnic group			P[a]	P[b]
	Europeans n = *57*	*Melanesians* n = *287*	*Polynesians* n = *48*		
FPG (mmol/l)	5.78 (5.62–5.93)	5.46 (5.38–5.54)	6.03 (5.89–6.18)	<0.0001	<0.0001
2h-PG (mmol/l)[c]	5.99 (5.59–6.42)	5.68 (5.50–5.87)	6.11 (5.72–6.53)	NS	<0.03
Glucose tolerance					
Normal	37 (64.9)	222 (77.4)	27 (56.3)	<0.01	<0.002
IFG	12 (21.1)	40 (13.9)	17 (35.4)		
IGT	8 (14.0)	25 (8.7)	4 (8.3)		
FPI (pmol/l)[c]	78.3 (63.0–97.3)	67.0 (60.6–74.1)	61.7 (49.7–76.6)	NS	<0.004
HOMA-IR[c]	3.33 (2.67–4.15)	2.68 (2.42–2.98)	2.75 (2.19–3.45)	NS	<0.002
HOMA-BC[c]	119.3 (94.7–150.3)	124.8 (112.2-138.9)	83.1 (68.0-101.5)	<0.02	<0.002

Abbreviations: FPG, fasting plasma glucose, FPI, fasting plasma insulin, HOMA-BC, homeostasis model assessment ß-cell secretory capacity, HOMA-IR, homeostasis model assessment of insulin resistance, IGT, impaired glucose tolerance, IFG, impaired fasting glucose, NS, not significant, 2h-PG, 2 h-plasma glucose. Values are means (95% confidence intervals) for continuous variables, or numbers (percentages) for categorical variables. [a]Crude. [b]Covariance analysis with age, sex and BMI as adjusted covariables. [c]Log-transform applied.

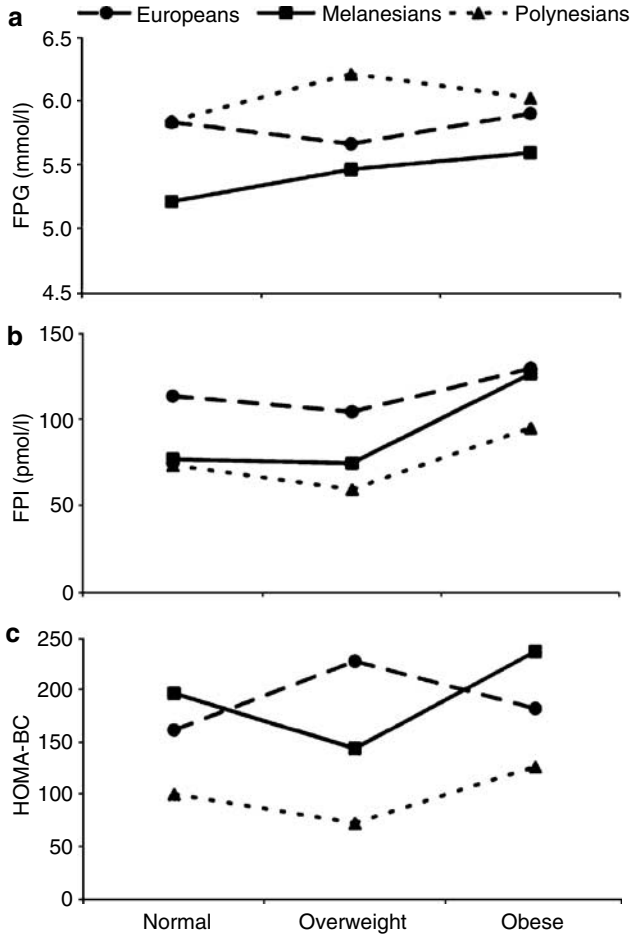

Figure 1 Levels of fasting plasma glucose (FPG, **a**), fasting plasma insulin (FPI, **b**) and HOMA estimate of β-cell function (HOMA-BC, **c**) by degree of overweight in nondiabetic Europeans, Melanesians and Polynesians in New Caledonia.

estimation of insulin secretion and insulin resistance, the HOMA indices have been validated against the glucose clamp, for various degrees of glucose tolerance and plasma insulin levels,[15] and have been largely used in epidemiological studies.[5,16]

Our results are consistent with those of Simmons *et al.*[5], who found that Polynesians of New-Zealand were not 'intrinsically insulin resistant' despite a high prevalence rate of diabetes and a greater central and overall obesity compared to Europeans of the same area. In their study, although Polynesians had significantly higher markers of insulin resistance in univariate comparisons, there were no differences after adjustment for BMI (in our study, this was the case even before adjustment for BMI).

Altogether, these two studies suggest that in Polynesians, the progression from normal glucose tolerance to type 2 diabetes may not include an insulin resistance state characterized by compensatory hyperinsulinaemia. It is already known that the pathogenesis of type 2 diabetes is a combination of insulin resistance and reduced insulin secretion,[2] and the predominant mechanism is possibly different in various ethnic groups.[4] Our study points out to pancreatic deficiency being the main anomaly taking part in the Polynesians' high susceptibility to diabetes mellitus. However, the absence of a frank defect of insulin sensitivity is unexpected, given their general morphotype, as excess adiposity is normally accompanied by insulin resistance[17] and decrease in insulin sensitivity is even considered a regulatory response to weight gain, which it serves to limit.[18] Of course, we cannot exclude that HOMA-IR is not a correct estimate of insulin resistance in this ethnic group, although it has been validated in subjects with normal to low insulin concentrations at least in one study.[15] Besides, fasting plasma insulin levels and insulin sensitivity are reciprocally related,[19] making it unlikely that Polynesians would actually be insulin resistant although they have normal insulin levels. If we consider that Polynesians are truly not insulin resistant, one explanation may be that BMI is not a good estimate of adiposity in this particular ethnic group. Indeed, the universal BMI standards for defining 'overweight' and 'obesity' in adults are based on the risk of adiposity-related diseases in Caucasians,[20] and this may not apply to all populations. For instance, in a meta-analysis about ethnic differences in the associations between BMI and per cent body fat, Polynesians had the highest mean BMI, whereas their degree of body fatness was below that of some ethnic groups such as Indonesians, Thais or Ethiopians.[21] Another study showed that, at higher BMI levels, Polynesians had significantly more lean mass than Europeans.[22] Another possible explanation is that, as Polynesians in New Caledonia are generally employed in heavy, energy-consuming work, this may significantly enhance their insulin sensitivity.[4,23] Also, it cannot be excluded that Polynesians have an insulin-deficient form of diabetes, different from type 2.[2,24,25]

Whatever the explanation, if it is confirmed that insulin resistance in the prediabetic state is not the prominent anomaly in this ethnic group (and maybe others), a new approach to the prevention of type 2 diabetes should be designed.

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