

## ABSTRACT

### NON-INSULIN DEPENDENT DIABETES MELLITUS AND INSULIN RESISTANCE IN JAMAICA; GENDER AND THE CONTRIBUTION OF THE TRP64ARG MUTATION OF THE $\beta$ -3 ADRENERGIC RECEPTOR GENE.

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NIDDM and other chronic cardiovascular diseases are contributors to the increase seen in morbidity and mortality rates in the Jamaican population. In Jamaica the prevalence of NIDDM overall, is 14.5% in the 25-74 age groups. The rate (17.8%) is higher in women compared to men (9%) (Cooper et al,1997). The relative contributions of insulin resistance (IR) and  $\beta$ -cell dysfunction (% $\beta$ -cell) to the aetiology of NIDDM remains controversial.

#### *Glycaemic status*

The study population was of predominantly African origin and was representative of the Jamaican population. To highlight differences in carbohydrate metabolism, sub-groups were chosen from the extreme ends (15%) of the normal distribution curve of 2-hour glucose values. Plasma levels of insulin and C-peptide were measured on the sub-groups (normoglycaemics; hyperglycaemics). Insulin resistance (IR) and  $\beta$ -cell dysfunction (% $\beta$ -cell function) were calculated using the HOMA model. The distribution of the fasting insulin/glucose ratio (IGR) in the normoglycaemic group was used to establish a reference interval. This was used to determine the number of individuals in the hyperglycaemic group that were either  $\beta$ -cell dysfunctional, insulin resistant or both. IGR correlated well with IR

( $r=0.89$ ) and with % $\beta$ -cell function ( $r=0.60$ ). 46.7% of the hyperglycaemic subjects had a low IGR suggesting decreased insulin production; 30.8% had high IGR indicating insulin resistance. The remaining 22.5% had a mixture of both. In the high IGR group, women outnumbered the men 3:1 . Using HOMA calculations IR and % $\beta$ -cell function were higher in the women. The women were younger, shorter, heavier and had larger BMI's, hip, waist and arm circumferences than the men. Insulin resistance contributes to the development of NIDDM but proportionately more so in the women.

### *Genetic Analyses*

The Trp64Arg mutation of the  $\beta$ -3adrenergic receptor gene ( $\beta$ -<sub>3</sub>AR) has been linked to earlier onset of NIDDM, insulin resistance, abdominal obesity and an increased capacity to gain weight in the Japanese and some European populations. The frequency of the Trp64Arg mutation and its association with NIDDM and IR was determined in a sample representative of the population. The allelic frequency of the Trp64Arg mutation of the  $\beta$ -3 adrenergic receptor gene was 10.5%. Significantly higher BMI, weight , fasting glucose, insulin, C-peptide and 2-hour glucose concentrations were associated with the presence of the mutation in women but not in men. Using simple regression analysis, fasting and 2-hour glucose levels were predicted by  $\beta$ -3 AR, age and some measures of adiposity. Hyperglycaemia and some measures of adiposity were associated with the presence of the Trp64Arg polymorphism. In the women, the Trp64Arg polymorphism plays a role either as a candidate or marker gene for the development of obesity and diabetes.