UNIVERSITI TEKNOLOGI MARA

UNRAVELLING THE PATHOPHYSIOLOGY OF OBESITY IN MALAY ADULT RESPONDENTS: INTEGRATION OF MULTIPLE DETERMINANT DATA USING GENOMICS AND METABOLOMICS APPROACHES

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ABSTRACT

Obesity is one of the most pressing problems in developed and developing countries, including Malaysia. The prevalence is increasing, thus urges the necessity in finding simple resolution to predict obesity, and subsequently prevent the co-morbidities effect such as CVD, T2DM, hypertension and cancers. Obesity is resulting from interaction between modifiable obesogenic factors such as lifestyle, diet, environment and behaviour, and endogenous genetic predisposition. Glucocorticoid receptor (GCR) activity plays a significant role in the aetiology of obesity and is essential for glucose homeostasis, the development of hyperinsulinaemia, and subsequent increase in fat deposition. There is insufficient knowledge of the GCR in metabolic conditions of obesity. Genetic variants present in GCR are believed to be associated with alteration in glucocorticoid sensitivity. In the present study, the specific features of obesity were compared between the obese and normal lean of the Malay adult respondents. A total of 130 obese (mean BMI, M = 32.90, SE = 0.47, 95% CI = 27.84–36.87) and 116 normal lean (BMI, M = 21.29, SE = 0.12, 95% CI = 18.51–22.84) respondents were evaluated for differences in anthropometric and socio-demographic, biochemical and hormonal determinants, genetics and metabolomics profile. Baseline characteristics were summarised for the samples, and appropriate linkages and integration between the multiple determinants data involved were investigated using genomics and metabolomics approaches. There was significant elevation of lipid profile and cortisol levels of the *BclI* and *N363S* SNPS of the obese respondents (p<0.05), suggesting the variants role with hypersensitivity of GC and involvement in the pathophysiology of obesity. In contrast, the *rs6194* has significantly decreased level of the lipid profile, HsCRP, cortisol, and other determinants, suggesting the protective effect of this variant towards the development of the obese phenotype. Thus, these loci can be potentially suggested as susceptible markers in the Malay Malaysian population. Early screening for these alleles is suggested to have merit in overall evaluation of a person's risk in developing obesity later in life. The LC/MS Q-TOF platform was used to carry out a global metabolite profiling in the obese and normal lean respondents. A list of differentially expressed metabolites was profiled using MPP software, ROCCET and MetPA analyses in tying up the biochemical process comparatively displaying the *NR3C1* gene function. A total of 49 from 225 metabolites were detected to be significant and differentially expressed between the obese and normal lean groups. Metabolites such as 4Z,7Z,10Z,13Z-eicosatetraenoic acid, 7,7-dimethyl-5Z,8Z,11Z-eicosatrienoic acid, 7-palmitoleic acid, phosphorylcholine, 21-deoxycortisol, dihydrocortisol, aldosterone, corticosterone, 25-dihydroxy-19-nor-22-oxavitamin D3, glucose and L-octaoylcarnitine have been highlighted as potential biomarkers for obesity in the present study. The role of these metabolites, mainly from the arachidonic acid metabolism and steroid biosynthesis were linked with the *NR3C1* gene, as this gene has also been associated with its overexpression in inflammatory stress and oxidative disorder. In conclusion, metabolomics approach has contributed in bridging the gap between the genotype and phenotype, and identifying novel changes in specific metabolites and pathways related to the pathophysiology of obesity.

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CHAPTER ONE
INTRODUCTION

1.1 Background

Obesity has become most pressing problem, in many developed and developing countries, including Malaysia. National Health and Morbidity Survey (2018) has reported the prevalence for overweight and obesity in Malaysia has increased to 47.7%. Although obesity is frequently associated with environmental factors such as diet and lifestyle, previous studies had proven that genetic factors also play an important role in the pathogenesis of obesity. Rare mutations in humans and model organisms have provided insights into the pathways involved in regulation of body weight. At the present time, risk predisposition to obesity has been quite extensively studied in candidate genes that indicate sequence variations of adrenergic receptors, uncoupling proteins, peroxisome proliferator-activated receptor and leptin receptor. The different in study population's findings of other countries and inconclusiveness of the results have encouraged us to further examine on the association of *NR3C1* gene polymorphisms with obesity in Malay adult population.

In the present study, screening of eight exonic regions of the *NR3C1* allows the identification of new and rare genetic variants among the subjects. Discovery of this SNP then leads to various studies correlating the *NR3C1* genotype with endogenous biochemical and hormonal data, nutritional intake and physical activity. Thus, it is crucial to identify the genetic variations harbouring considerable potential as biomarkers for the monitoring of obesity and its associated co-morbidities such as cardiovascular disease, diabetes and hypertension. Owing to this fact, the differential profiles of metabolites among the obese and lean respondents were also studied. The significant pathways involved was then proposed and correlated with the present data. These are useful in providing understanding on the pathogenesis of obesity.

Although understanding of the specific features of obesity in Asia is increasing, little is known about the underlying pathophysiology of obesity. With this element boundary, therefore, in the present study, the specific features of obesity were compared between the obese and normal lean of the Malay respondents. These include the significant anthropometric-sociodemographic, biochemical and hormonal