



The Role of Polymorphism Gly972Arg IRS-1 Gene and C981T PTP-1B Gene on Insulin Resistance Young Adult Subjects with Low Birth Weight History

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ABSTRACT

Insulin resistance is including birth defects, insulin role in the fetus and Barker hypothesis, genotype thrifty, but all of these hypotheses suggest that low birth weight is places of exposure for a permanent metabolic abnormality. The Changes in the nature of IRS-1 causes insulin signal transduction disturbance, one of which is Gly972Arg gene polymorphism IRS-1 (Gly change Arg in codon 972). Transduction of insulin signaling of other pathways through a process of phosphorylation involving tyrosine phosphatase-1B protein (PTPN-1B / PTP-1B) . This study aims to study the role of polymorphism Gly972Arg gene IRS-1 and C981T PTP-1B gene on insulin resistance of young adult subjects with history of LBW. The research design was historical cohort study. Insulin resistance was measured according to the HOMA-IR formula. Gly972Arg gene polymorphism IRS-1 and C981T PTP1B gene analysis using the PCR-RLFP method using the enzyme smaI and Eval. Polymorphism Gly972Arg gene IRS-1 was risk factor to develop insulin resistance. Low birth weight and polymorphism C981T gene PTP-1B were not risk factor to develop insulin resistance.

Keywords: Polymorphism Gly972Arg IRS-1, Polymorphism C981T PTP-1B, Insulin Resistance, Low Birth Weight

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INTRODUCTION

Insulin resistance is defined as the inability of cells to make sugar into the cells by involving the interactions of proteins and increased blood sugar levels throughout the cells in the human body [1, 2]. During pancreatic-β cells in perfect condition, insulin resistance only shows hyperinsulinemia [3]. The impairment of pancreatic-β cells because of intra uterine malnutrition will interfere with glucose tolerance to diabetes [4-7]. Overweight must not always experience with insulin resistance and vice versa, not all insulin resistance must be overweight. The prevalence of insulin resistance in India ranges from 20-55%, whereas the prevalence of insulin resistance in post-puberty children with a normal body mass index (BMI) is 20% -21.3% [8, 9].

Hypotheses of insulin resistance are include birth defects, insulin role in the fetus and Barker hypothesis, genotype thrifty [10, 11], but all of these hypotheses suggest that low birth weight is places of exposure for a permanent metabolic abnormality. Study argued that malnutrition at the time of fetus was illustrated by a history of LBW, associated with insulin resistance [12-14]. Molecular pathway of Insulin transduction involves insulin receptors substrates-1 (IRS-1) and other proteins [15-17]. In insulin resistance, the failure of signal transduction and sugar metabolism become abnormal. The Changes in the nature of IRS-1 causes insulin signal transduction disturbance, one of which is Gly972Arg gene polymorphism IRS-1 (Gly change Arg in codon 972) [18, 19]. Gly972Arg gene polymorphism IRS-1 gene is associated with insulin resistance, although, there is still controversy related Gly972Arg gene polymorphism IRS-1. It was thought to be a risk factor for insulin resistance [20].

Transduction of insulin signaling of other pathways through a process of phosphorylation involving tyrosine phosphatase-1B protein (PTPN-1B / PTP-1B) . In muscle of patients with diabetes melitus type 2 (DMT2) there is an increase in protein phosphatase such as PTP-1B. If PTP -1B undergoes polymorphism then insulin signal signaling will persist [21-24]. Gly972Arg Gly972Arg gene polymorphisms IRS-1 gene can be called insulin resistance risk factor and C981T polymorfism PTP-1B gene can be called as insulin resistance protection factor . Individuals on the genetic basis of Gly972Arg gene polymorphism of IRS-1 gene and or with no C981T gene polymorphism of PTP-1B gene were thought to be easier and younger for insulin resistance, did not require an increase weight until obese to develop into insulin resistance. Another study concluded that LBW is associated with increased fasting blood sugar and fat cell mass in African- American as well as increased mortality and as a predisposing factor of insulin resistance [25-27]. This study aims to study the role of polymorphism Gly972Arg gene IRS-1 and C981T PTP-1B gene on insulin resistance of young adult subjects with history of LBW.

MATERIALS AND METHODS

The research design was historical cohort study. Subject of study has birthweight note, born in 1988-1989 in Tanjungsari sub-district, West Java, Indonesia. Low birth weight (LBW) was birth weight equal to 2500 grams or less than 2500 grams regardless of gestational age. Selection of samples through simple random samples by wiring through computer data. Selected subject of 197 subjects consisted of 97 subjects of LBW group and 100 normal birth weight group. Subjects with growth and developmental disorders that influenced by other genetic factors, such as Mongolid or mental retardation or Noonan Syndrome, were exclude from the study.

Insulin resistance was measured according to the HOMA-IR formula $(FPIuU / ml \times FPG \text{ mmol} / l) / 22.5$. Insulin resistance were indicated when the value of HOMA-IR > 2.7. Gly972Arg gene polymorphism The IRS-1 gene is an IRS-1 gene polymorphism when Glycine changes to Arginine in the 972th codon sequence. An IRS-1 gene genotype analysis using the PCR-RLFP method using the enzyme smaI, called polymorphism when C allele is cut is obtained 183 pb, 153 pb and 80 pb fragments, if C allele is not truncated

resulting in fragments of 153 pb and 80 pb is normal(wild type).

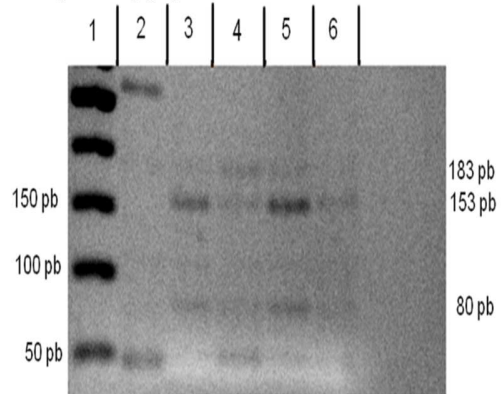


Figure 1: Results of PCR gene Product Gene IRS-1 with Enzym SmaI

C981T gene polymorphism PTP-1B gene is a PTP-1B gene polymorphism in which the base nucleotide base C (cytosine) is converted to T (Thymin) a third base on the order of nucleotide base to-98. Analysis of genotype of PTP-1B gene by PCR-RFLP method using AvaI restriction enzyme, called polymorphism if T allele is not cut is seen fragment of 330 pb and if C allele is cut, yielding fragment of 237 pb and 93 bb is normal gene (wild type).

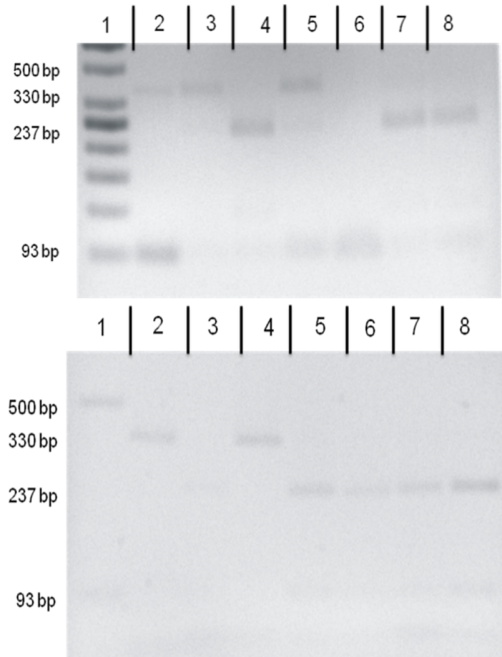


Figure 2: Results of PCR gene Product Gene PTP-1B with Enzyme AvaI

Table 1: Prevalence Insulin Resistance in Lower Birth Weight Group and Normal Birth Weight Group

Variable	Insulin Resistance		No Insulin Resistance		Total		X ²	P value*
	n	%	n	%	n	(%)		
Lower Birth Weight	3	3,1	94	96,90	97	49,24	0,12	0,517
Normal Birth Weight	4	4	96	96	100	50,76		
Total	7	3,55	190	96,45	197	100		

*Fisher Exact Test, p<0,05

Table 2: Baseline Characteristic

Variable	Group	n	Min	Max	Mean	SD	P value*
Waist Circumference (cm)	Lower birth weight	97	56,20	91,25	68,81	7,57	0,114
	Normal birth weight	100	56,00	99,55	70,49	7,31	
BMI(kg/m ²)	Lower birth weight	97	15,28	29,42	20,31	3,24	0,272
	Normal birth weight	100	16,36	32,47	20,80	3,01	
Fasting blood glucose (mg/dl)	Lower birth weight	97	70	118	86,19	7,63	0,821
	Normal birth weight	100	66,0	146	85,90	7,63	
Fasting Insulin level (uU/ml)	Lower birth weight	97	2,00	340	8,46	34,26	<0,001
	Normal birth weight	100	2,00	17,50	4,62	3,52	

*T test, p< 0,05

Table 3: Regression Analysis of Polymorphism Gly972Arg gene IRS-1, Polymorphism C981T gene PTP-1B and Low Birth Weight Related Insulin Resistance

Variable	Koefisien β	SE	P value*	RR	95% CI
Low Birth Weight	0,273	0,815	0,737	1,31	0,27-6,49
Polymorphism Arg972Gly gene IRS-1	2,100	0,813	0,010	8,17	1,66-40,16
Polymorphism C981T gene PTP-1B	-0,321	0,816	0,694	0,73	0,15-3,59

*Logistic Regression Test, P<0,05

RESULTS

Baseline Characteristic

The mean of age from subjects was 20,54±0,62 years. The mean of waist circumference was 69,11±7,15 cm. The mean of body mass index was 20,30±3,03 kg/m². The mean of fasting blood glucose and insulin level was 85,95±9,06 mg/dL and 6,31± 4,17 uU/mL.

Around 9,65% (19 subjects) had polymorphism Gly972Arg gene IRS-1 and 46,7% (92 subjects) had polymorphism C981T gene PTP-1B.

Polymorphism Gly972Arg gene IRS-1 was risk factor to develop insulin resistance. Low birth weight and polymorphism C981T gene PTP-1B were not risk factor to develop insulin resistance.

DISCUSSION

The prevalence of insulin resistance in the LBW group was lower than the normal birth weight group (3.10% vs 4%), in contrast to the results of previous investigators. The study gained prevalence of insulin resistance in post-puberty

subjects by 21.8% (male) and 35.8% (female) [15]. Insulin resistance was observed when subjects aged between 19-20 years, were not at birth. Insulin resistance in young adulthood can be due to various factors. The examination of insulin resistance using HOMA-IR formulation depends on fasting blood sugar and plasma insulin may be affected by weight factor, BMI, or abdominal circle.²⁰ The mean of waist circumference and BMI in the normal birth weight group was greater than the LBW group, there was significant difference (p> 0,05), whereas insulin secretion by β -pancreas cells between group of normal and low birth weight was significant difference. The LBW group had higher insulin levels than the normal birth weight group with fasting blood glucose level, but there was no significant difference in both groups. LBW subjects require greater insulin to achieve fasting blood sugar levels within normal limits. It was concluded that in LBW insulin resistance occurred and may be more severe than the normal birth weight group although the prevalence of insulin resistance in LBW group is lower than the normal birth weight group. LBW subjects have waist circumference and BMI was smaller than normal birth weight

group. It meant that in the LBW group there was no potential factor of insulin resistance, but if the LBW group with hyperinsulinemia was very susceptible to insulin resistance when the excessive metabolic load continues, according to other researchers that LBW is a risk factor of insulin resistance [20-23].

The Gly972Arg gene polymorphism study of IRS-1 gene has a higher chance of insulin resistance than LBW and has an 8.17 times greater chance of insulin resistance than subjects with a natural IRS-1 gene, meaning Gly972Arg gene of IRS-1 gene is a major factor in insulin resistance was confirmed by the prevalence of Gly972Arg gene of IRS-1 gene on LBW greater than normal birth weight. Excessive nutrition and increased obesity, genetic factors as well as interactions with environmental factors of both motherhood and childhood will affect childhood growth against early development of adult disease risk. Gly972Arg variant of IRS-1 gene is thought to be due to LBW or vice versa the variant precedes LBW. The mechanism of Gly972Arg variant of the IRS-1 gene is still debated today [25-28]. Overall Gly972Arg gene polymorphisms IRS-1 gene is a dominant risk factor for insulin resistance.

CONCLUSION

Polymorphism Gly972Arg gene IRS-1 was risk factor to develop insulin resistance. Low birth weight and polymorphism C981T gene PTP-1B were not risk factor to develop insulin resistance.

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