Polimorfisme Gen *Cyclin-dependent kinase 5 Regulatory Associated Protein 1-like* (*CDKAL1*), Pola Makan dan Risiko Diabetes Melitus Tipe 2 pada Etnis Minahasa dan Sumba

ABSTRAK

Latar belakang: Diabetes melitus merupakan penyakit multifaktor, yang melibatkan interaksi kompleks antara lingkungan dan genetik. Pola makan dan faktor genetik berperan signifikan terhadap diabetes melitus tipe 2. Studi genetik menunjukkan bahwa pengaruh gen terhadap diabetes bervariasi antar etnis. Gen *CDKAL1* banyak diteliti karena keterkaitannya dengan diabetes melitus tipe 2. Meskipun variasinya ditemukan pada berbagai etnis, efek alelnya dapat berbeda. Pada populasi Asia, frekuensi alel risiko gen ini lebih tinggi dibandingkan Eropa.
Tujuan Penelitian: Menganalisis hubungan polimorfisme gen *CDKAL1* (rs7756992, dan rs10946398) dan pola makan dengan kejadian diabetes melitus tipe 2 pada etnis Minahasa dan Sumba di Indonesia.
Metode: Penelitian ini merupakan penelitian observasional dengan desain *case-control*. Pada semua partisipan dilakukan penilaian pola konsumsi, aktivitas fisik, pengukuran tinggi badan, berat badan, lemak tubuh, pemeriksaan kadar gula puasa, HOMA-IR, HOMA β dan profil lipid. Variasi genetik *CDKAL1* dilihat pada rs7756992 dan rs10946398.
Hasil: Terdapat perbedaan frekuensi genotipe dan alel pada etnis Minahasa dan Sumba ($p<0,05$). Alel risiko G (rs7756992) dan C (rs10946398) lebih banyak ditemukan pada etnis Sumba dibandingkan Minahasa. Analisis berdasarkan jenis kelamin menunjukkan bahwa pada laki-laki Minahasa, genotipe AG rs7756992 ($p = 0,019$) dan AC rs10946398 ($p = 0,031$) berhubungan signifikan dengan peningkatan risiko DM tipe 2. Sementara itu, pada perempuan Sumba, genotipe CC rs10946398 juga meningkatkan risiko secara signifikan ($p = 0,030$). Asupan energi, lemak, dan karbohidrat lebih tinggi pada kelompok kasus di Minahasa. Sedangkan di Sumba asupan energi dan seluruh makronutrien lebih tinggi pada kelompok kasus. Meskipun pola makan lokal mendominasi pada kedua kasus, namun pada Minahasa pola makan barat lebih menonjol dibandingkan di Sumba. Pada etnis Minahasa, kombinasi genotipe AG-GG rs7756992 dengan asupan energi tinggi meningkatkan risiko DM tipe 2 secara signifikan (OR = 8,16; 95% CI: 1,105–60,307; $p = 0,04$). Nilai interaksi aditif sebesar 6,01 dan multiplikatif sebesar 4,76 mengindikasikan adanya efek sinergistik antara gen dan diet
Kesimpulan: Ada perbedaan frekuensi genotipe dan alel pada kedua etnis, dimana alel risiko lebih sering ditemukan di etnis Sumba. Meskipun tidak ditemukan hubungan signifikan secara keseluruhan, genotipe AG dan AC pada laki-laki Minahasa serta CC dan alel C pada perempuan Sumba meningkatkan risiko DM tipe 2 secara signifikan. Asupan makanan pada kelompok kasus dan kontrol berbeda secara signifikan pada kedua etnis. Tidak semua asupan makanan berinteraksi dengan *CDKAL1* dan arah interaksinya juga tidak selalu sinergis

Kata kunci: *diabetes melitus, pola makan, CDKAL1, rs7756992, rs10946398*

ABSTRACT

Polymorphism Gen *Cyclin-dependent kinase 5 Regulatory Associated 1-like Protein* (*CDKAL1*), Diet and Risk of Type 2 Diabetes Mellitus on the Minahasa and Sumba Ethnicities

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Background: Diabetes mellitus is a multifactorial disease, which involves complex interactions between the environment and genetics. Diet and genetic factors play a significant role in type 2 diabetes mellitus. Genetic studies show that the influence of genes on diabetes varies between ethnicities. The *CDKAL1* gene is widely studied for its association with type 2 diabetes. Although the variation is found in different ethnicities, the allele effects can be different. The frequency of risk alleles is higher in Asian populations than in Europe. **Objective:** To analyze the relationship between *CDKAL1* gene polymorphism (rs7756992, and rs10946398) and diet with the incidence of type 2 diabetes in Minahasa and Sumba ethnicities in Indonesia. **Methods**: This study is an observational study with case control design. All participants were assessed on consumption patterns, physical activity, height measurement, weight, body fat, fasting sugar levels, HOMA-IR, HOMA β and lipid profiles. Genetic variation of *CDKAL1* was seen in rs7756992 and rs10946398. **Results:** There was a difference in genotype and allele frequencies in Minahasa and Sumba ethnicities ($p<0.05$). The risk alleles G (rs7756992) and C (rs10946398) are more common in ethnic Sumba than in Minahasa. Analysis by sex showed that in Minahasa males, the genotypes of AG rs7756992 ($p = 0.019$) and AC rs10946398 ($p = 0.031$) were significantly associated with an increased risk of type 2 DM. Meanwhile, in Sumba women, the CC genotype rs10946398 also significantly increased the risk ($p = 0.030$). Energy, fat, and carbohydrate intake was higher in the case group in Minahasa. In Sumba, energy intake and all macronutrients were higher in the case group. Although the local diet dominates in both cases, in Minahasa the western diet is more prominent than in Sumba. In the Minahasa ethnicity, the combination of the AG-GG genotype rs7756992 with high energy intake significantly increased the risk of type 2 DM (OR = 8.16; 95% CI: 1.105–60.307; $p = 0.04$). The additive interaction value of 6.01 and the multiplier of 4.76 indicated a synergistic effect between genes and diet. **Conclusion:** There is a difference in the frequency of genotypes and alleles in both ethnicities, where risk alleles are more commonly found in the Sumba ethnicity. Although no overall significant association was found, the genotypes of AG and AC in Minahasa males as well as CC and C alleles in Sumba females significantly increased the risk of type 2 DM. Food intake in the case and control groups differed significantly in both ethnicities. Not all food intake interacts with *CDKAL1* and the direction of interaction is also not always synergistic

Keywords: *diabetes mellitus, diet, CDKAL1, rs7756992, rs10946392*