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Relation Of The Quadrumvirate — Hepatic Steatosis, High Normal Fasting Glucose, And Attenuated Whole Body-insulin Sensitivity And Glucose-stimulated Acute Insulin Secretion — To Incident Prediabetes, The Beginning Of Type 2 Diabetes

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Type 2 diabetes begins as conversion of normal glucose metabolism (NGM) to prediabetes, and 5-10% per year of people with prediabetes progress to diabetes. Therefore, understanding evolution of prediabetes is mandatory to know how type 2 diabetes starts. However, the process of conversion of NGM to prediabetes, which may be ethnicity-specific, has poorly been investigated. We analyzed 599 Japanese adults with NGM (fasting plasma glucose (FPG) <100 mg·dL-1 and 2-h PG at 75 g oral glucose tolerance (OGTT) <140 mg·dL-1) (male 62%, the mean age, body mass index (BMI), fasting IRI/FPG and 2-h IRI/PG, 52 years, 23.1 kg·m-2, 4.1 μU·mL-1/92 mg·dL-1 and 24.5 μU·mL-1/104 mg·dL-1, respectively). They received follow-up OGTTs at a mean of 3.7 years later (2,061 person-years observation). Prediabetes developed in 179 (impaired fasting glucose 102, impaired glucose tolerance 39, and impaired fasting glucose/impaired glucose tolerance 28). By the screening univariate analysis, Fatty Liver Index (FLI), FPG, ISIMATSUDA (index of basal and post-glucose whole body insulin sensitivity (Si) and Stumvoll's first phase (Stumvoll-1, an index of glucose-stimulated acute (~10 min) insulin secretion (Isec) were robust risk factors for incident prediabetes. In contrast, indices of basal Si such as HOMA-IR, and basal, 30 min, or later phase index of Isec such as HOMAbeta and insulinogenic index, respectively, were not significant risk for prediabetes. In multivariate Cox model adjusted for age and sex, HR (95%CI) per 1 IQR increase were FLI 1.303 (1. 063-1.586), P <0. 01; FPG 1.400 (1. 076-1.840), P <0. 01; ISIMATSUDA 0.841 (0.712-0.963), P = 0. 03; Stumvoll-1 0.764 (0.622-0.935) P <0. 01. Note that FLI and FPG are risk factors and ISIMATSUDA and Stumvoll-1 are protective factors. Notably, FLI was a risk even after adjustment for BMI. The best cutoff values differentiating prediabetes Progressors from Nonprogressors obtained by the ROC curve using entire range of each risk factor was ≥12.4 for FLI, ≥95 mg·dL-1 for FPG, ≤11.99 for ISIMATSUDA and ≤486.3 for Stumvoll-1, and incidence of prediabetes was

progressively high as 10/127 (6%), 34/153 (22%), 56/189 (30%), 53/106 (50%) and 16/24 (67%) among the participants with no, one, two, three and four unfavorable discriminating values for progression, respectively. AUC of ROC curve (AUROC) for the combination of the quadrumvirate was as large as 0.729 (0.661-0.788) with high precision as sensitivity 73.4% and specificity 63.8%. In conclusion, at the beginning of type 2 diabetes in the Japanese population who are non-obese and insulin-sensitive as shown, hepatic steatosis, the high normal FPG, attenuation of whole-body insulin sensitivity, lowered acute phase glucose-induced insulin release (the quadrumvirate) are synergistically and independently, with comparable strength each other, related to the development of prediabetes.

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