Case Control Study

Pancreatic hyperechogenicity associated with hypoadiponectinemia and insulin resistance: A Japanese population study

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Abstract

AIM
To examine the relationship between pancreatic hyperechogenicity and risk factors for metabolic syndrome.

METHODS
A general population-based survey of lifestyle-related diseases was conducted from 2005 to 2006 in Japan. The study involved 551 participants older than 40 year of age. Data for 472 non-diabetic adults were included in the analysis. The measures included the demographic factors, blood parameters, results of a 75 g oral glucose tolerance test, and abdominal ultrasonography. The echogenicity of the pancreas and liver was compared, and then the subjects were separated into two groups: cases with pancreatic hyperechogenicity ($n = 208$) and cases without (controls, $n = 264$). The differences between both groups were compared using an unpaired $t$-test or Fisher’s exact test. Multiple logistic regression analysis was used to determine the relationship between the pancreatic hyperechogenicity and clinical and bio-
Pancreatic hyperechogenicity; Metabolic syndrome; Obesity; Adiponectin; The Takahata study

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Core tip: Pancreatic hyperechogenicity is related to aging. Several recent studies have reported that hepatic steatosis and increased body mass index (BMI) are predictors of a hyperechogenic pancreas. In the present study, fatty liver was also significantly associated with pancreatic hyperechogenicity. We performed additional analyses excluding participants with fatty liver in order to account for the effect of this condition. Our analyses showed that an increased BMI, higher homoeostasis model assessment of insulin resistance score, and decreased adiponectin were also significantly associated with pancreatic hyperechogenicity.

INTRODUCTION
Pancreatic hyperechogenicity may be related to the aging process. Previous studies have reported that increased echogenicity of the pancreas is associated with pancreatic lipomatosis. Additionally, recent ultrasound studies have demonstrated pancreatic hyperechogenicity is correlated with obesity, hepatic steatosis, and insulin resistance. To our knowledge, there are a limited number of reports examining the relationship between pancreatic hyperechogenicity and lifestyle-related risk factors.

Recent studies have demonstrated that adipose tissue not only stores fat but also functions as an endocrine organ by producing various adipocytokines such as adiponectin. Adiponectin is a peptide hormone that plays a key role in the development of insulin resistance associated with metabolic syndrome. Adiponectin levels are correlated directly with insulin sensitivity and are decreased in obese individuals and patients with type 2 diabetes. Recent studies have shown that there is an association between low concentrations of adiponectin and cancer development. However, no report has examined the relationship between adiponectin concentration and pancreatic hyperechogenicity.

The aim of the present study was to examine the associations between pancreatic hyperechogenicity and risk factors for metabolic syndrome, including adiponectin concentration, in the general Japanese population.

MATERIALS AND METHODS

Study population
The study was part of an ongoing molecular epidemiological project utilizing the regional characteristics of the 21st Century Centers of Excellence program in Japan, which has been previously described. The surveyed population was the entire population of adults aged over 40 year in the town of Takahata, Yamagata prefecture, located in northeastern Japan. There were 551 participants enrolled in the study between 2005 and 2006. All participants received a physical examination, blood tests, a 75-g oral glucose tolerance test (OGTT), and abdominal ultrasonography (US). We excluded 79 of the 551 participants for the following reasons: Poor US images of the pancreas (43 individuals); blood samples collected in a non-fasting state (27 individuals); or OGTT-diagnosed diabetes mellitus based on the American Diabetes Association criteria (9 individuals). Exclusion criteria included a history of diabetes or pancreatic disease. However, no participants met the exclusion criteria. The data collected from 472 subjects (201 males and 271 females) were included in the final analysis.

Measurements
We obtained information on current medication and lifestyle-related characteristics from all participants using a questionnaire. Trained study staff measured height, weight and systolic and diastolic blood pressure (BP) using standard methods. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters squared). Insulin resistance was evaluated using
the homeostasis model assessment of insulin resistance (HOMA-IR) method with the following equation: HOMA-IR = fasting insulin (µU/mL) × fasting glucose (mg/dL)/405. Venous blood was drawn the morning after an overnight fast. The serum and plasma were separated immediately and stored at -80 °C until analysis. The serum adiponectin concentrations were measured by an enzyme-linked immunosorbent assay as described previously[5]. The other biochemical blood parameters were determined by standard laboratory procedures in the General Laboratory of BML, Inc. (Saitama, Japan). All laboratory personnel were blinded to the status of the samples.

All participants underwent US and an OGTT during a single visit at the research center and within 2 mo of the physical examination and initial blood collection. Blood samples were obtained to determine plasma glucose in the basal period and 120 min after an oral glucose load in the morning following an overnight fast. The participants fasted overnight for the US study, and the scans were performed by one of four experienced operators using either a Toshiba NemioTM scanner or an Aloka SSD-3500 scanner with a 3.5-MHz convex transducer. The participants were scanned while lying supine. The images were recorded on a standard computer hard disk drive. The recorded images were analyzed and judged simultaneously by four experienced physicians blinded to the details of the subjects, as described in a previous report[5]. The echogenicity of the pancreatic body was compared with the liver. The subjects were separated into cases with pancreatic echogenicity higher than hepatic echogenicity (n = 208) and controls whose pancreatic echogenicity was equal to or lower than the liver (n = 264). The presence of fatty liver was defined as a US pattern consistent with liver steatosis, i.e., narrowing of the lumen of the hepatic veins. We used these criteria to divide the subjects into cases with (n = 206) or without (n = 266) fatty liver.

Statistical analysis

The distribution of the continuous variables was assessed for normality. If a normal distribution was evident, then the data were expressed as the means ± standard deviation. The data with a non-normal distribution were log-transformed for analysis and expressed as the means ± standard deviation. The data with a non-normal distribution were log-transformed for analysis and expressed as the means ± standard deviation. The data with a non-normal distribution were log-transformed for analysis and expressed as the means ± standard deviation. The data with a non-normal distribution were log-transformed for analysis and expressed as the means ± standard deviation.

RESULTS

The baseline clinical and biochemical data for the cases and controls are shown in Table 1. The serum adiponectin levels were markedly lower in the cases than in the controls [8.9 (6.5-12.8) vs 11.1 (7.8-15.9), P < 0.001]. In addition, there were significant differences between the cases and controls for the following variables: Age, presence of fatty liver, weight, BMI, systolic BP, diastolic BP, serum insulin, fasting plasma glucose, HOMA-IR score, HDL cholesterol, total cholesterol, triglyceride, pancreatic isoamylase, GPT, pre-load plasma glucose in the OGTT, and 2-h plasma glucose. Each parameter was dichotomized according to the cutoff points to further explore the relationship between pancreatic hyperechogenicity and other parameters. We then conducted multiple logistic regression analyses with the backward elimination method.

We first used an age-adjusted model to exclude the influence of aging. The results indicate that there was a significant negative association between decreased adiponectin levels and pancreatic hyperechogenicity (OR = 0.92, 95%CI: 0.88-0.95, P < 0.001). In addition, the presence of fatty liver, higher values of BMI, systolic BP, diastolic BP, serum insulin, HOMA-IR score, 2-h plasma glucose, 2-h plasma glucose, and lower pancreatic isoamylase levels were significantly associated with pancreatic hyperechogenicity (Table 2).

We next performed the analysis after adjustment for age, presence of fatty liver, BMI, systolic and diastolic BP, adiponectin, serum insulin, HOMA-IR, triglyceride, pancreatic isoamylase, GPT, and 2-h plasma glucose. The analysis showed that hypoadiponectinemia was significantly associated with pancreatic hyperechogenicity (OR = 0.9, 95%CI: 0.91-0.98, P = 0.004), independent of the other confounding variables. The presence of fatty liver, increased BMI, and higher HOMA-IR score were also significantly associated with pancreatic hyperechogenicity. In addition, decreased pancreatic isoamylase showed a weak relationship with pancreatic hyperechogenicity (Table 2).

We then performed further analyses to exclude the influence of fatty liver. The baseline clinical and...
biochemical data for cases and controls without fatty liver are shown in Table 3. The serum adiponectin levels were lower in cases than in controls (10.3 (7.6-14.6) vs 12.0 (8.6-17.0), P = 0.022). Furthermore, there were significant differences between cases and controls for the following parameters: Age, weight, BMI, serum insulin, fasting plasma glucose, HOMA-IR score, HDL cholesterol, triglycerides, and preloading plasma glucose in the OGTT.

We next performed multivariate association analyses of data from participants without fatty liver. The multivariate analysis showed that hyposalpinopenemia was significantly associated with pancreatic hyperechogenicity (OR = 0.93, 95%CI: 0.90-0.97, P < 0.001), independent of the other confounding variables. Additionally, an increased BMI and higher HOMA-IR score were also significantly associated with pancreatic hyperechogenicity (Table 4).

**DISCUSSION**

Studies examining digestive organ disease and altered...
secretion of adipocytokines caused by metabolic syndrome will improve our understanding of the mechanisms involved in pathophysiological conditions. It is possible that such investigations might lead to the development of preventive measures for diseases linked to metabolic syndrome.

Pancreatic hyperechogenicity is thought to be related to the aging process\(^\text{[1-3]}\). Our data showed that several features of metabolic syndrome, such as higher BMI, increased HOMA-IR score, and hypoadiponectinemia, were also independently associated with pancreatic hyperechogenicity.

This is the first study conducted in a general population that investigated the relationship between pancreatic hyperechogenicity and risk factors of metabolic syndrome, such as insulin resistance and serum adiponectin concentration. The main study findings were: (1) that serum adiponectin concentrations were markedly lower in subjects with pancreatic hyperechogenicity than in controls \(8.9 \pm 12.8\) vs \(11.1 \pm 15.9\), \(P < 0.001\); and (2) that decreased adiponectin levels were associated independently with pancreatic hyperechogenicity (OR = 0.9, 95%CI: 0.91-0.98, \(P = 0.004\)). Adiponectin is produced by adipose tissue, and a low adiponectin concentration is considered to be a key factor in the development of insulin resistance underlying metabolic syndrome\(^\text{[4-11]}\).

Several studies have reported that increased echogenicity of the pancreas is related to lipomatosis of the pancreatic parenchyma\(^\text{[6-8,16-19]}\). Pancreatic lipomatosis is the most common histological change in the pancreas associated with age, obesity, and insulin resistance\(^\text{[8-10,16-19]}\). Recently, Raeder et al\(^\text{[20]}\) evaluated the pancreatic fat content using US and magnetic resonance imaging and showed that pancreatic lipomatosis may reflect early events involved in the pathogenesis of diabetes and exocrine pancreatic dysfunction in non-diabetic children with mutations in carboxyl-ester lipase. In addition, Tushuizen and co-workers\(^\text{[20]}\) measured the pancreatic fat content using proton magnetic resonance spectroscopy and found that pancreatic fat was inversely associated with \(\beta\)-cell function parameters in non-diabetic men. However, there was no association in their diabetic counterparts. The authors suggested that pancreatic fat content may contribute to \(\beta\)-cell dysfunction\(^\text{[20]}\).

In our logistic regression analysis, we adjusted for age and pancreatic hyperechogenicity, which is a potential marker of lipomatosis. We found that these parameters were associated with higher serum insulin, HOMA-IR, and 2-h plasma glucose levels in the OGTT. This was

### Table 3: Comparison of baseline characteristics between the pancreatic hyperechogenicity and control groups excluding participants with fatty liver

| Clinical parameters | Pancreatic hyperechogenicity (\(n = 95\)) | Control (\(n = 171\)) | \(P\) value |
|---------------------|-----------------------------------------|-----------------------|------------|
| Age (yr)            | 62 ± 9                                  | 58 ± 10               | 0.001      |
| Sex (male/female)   | 44/51                                   | 76/95                 | 0.769      |
| Height (cm)         | 158.0 ± 8.0                             | 158.1 ± 9.0           | 0.960      |
| Weight (kg)         | 59.5 ± 9.4                              | 53.9 ± 8.5            | < 0.001    |
| BMI (kg/m²)         | 23.7 ± 2.6                              | 21.5 ± 2.5            | < 0.001    |
| Systolic BP (mmHg)  | 133 ± 17                                | 130 ± 16              | 0.135      |
| Diastolic BP (mmHg) | 82 ± 11                                 | 80 ± 10               | 0.130      |
| Adiponectin (µg/mL) | 10.3 (7.6-14.6)                         | 12.0 (8.6-17.0)       | 0.022      |
| Serum insulin (µU/mL) | 4.0 (2.7-5.4)                       | 3.3 (2.5-4.5)         | 0.004      |
| Fasting plasma glucose (mg/dL) | 93 ± 8                                    | 90 ± 10               | 0.026      |
| HOMA-IR             | 0.9 (0.59-1.28)                         | 0.71 (0.54-1.02)      | 0.002      |
| High-density lipoprotein cholesterol (mg/dL) | 60 ± 15                                  | 66 ± 15               | 0.001      |
| Low-density lipoprotein cholesterol (mg/dL) | 124 ± 35                                 | 122 ± 33              | 0.708      |
| Total cholesterol (mg/dL) | 202 ± 33                                 | 199 ± 36              | 0.464      |
| Triglyceride (mg/dL) | 87 (66-133)                             | 76 (59-96)            | 0.005      |
| Pancreatic isoamylase (IU/L) | 29 (24-35)                               | 31 (25-37)            | 0.054      |
| Glutamic oxaloacetic transaminase (IU/L) | 22 (19-25)                                | 23 (19-28)            | 0.189      |
| Glutamic pyruvic transaminase (IU/L) | 19 (16-23)                                | 20 (15-25)            | 0.937      |
| γ-glutamyl transpeptidase (IU/L) | 21 (16-40)                               | 21 (15-32)            | 0.266      |
| Preload plasma glucose (OGTT) (mg/dL) | 96 ± 9                                   | 92 ± 10               | 0.009      |
| 2-h plasma glucose (OGTT) (mg/dL) | 107 ± 29                                 | 100 ± 28              | 0.063      |

Data are expressed as means ± SD, or median (25\(^{\text{th}}\); 75\(^{\text{th}}\) percentiles). Unpaired t test or Fisher’s exact test were used to compare the two groups. BMI: Body mass index; BP: Blood pressure; HOMA-IR: Homeostasis model assessment of insulin resistance; OGTT: Oral glucose tolerance test.

### Table 4: Multivariate association analysis of clinical parameters for pancreatic hyperechogenicity excluding participants with fatty liver

| Confounding factor | Multivariate \(^5\) | Odds ratio (95%CI) | \(P\) value |
|--------------------|---------------------|--------------------|------------|
| BMI (kg/m²)\(^4\) |                     | 3.89 (2.39-6.35)   | < 0.001    |
| Adiponectin (µg/mL)\(^3\) |               | 0.93 (0.90-0.97)   | < 0.001    |
| HOMA-IR            | 2.23 (1.02-4.89)    | 0.045              |            |

\(^{1}\)Serum adiponectin was analyzed as a continuous variable; \(^{3}\)Adjusted for age, BMI, diastolic BP, adiponectin, serum insulin, HOMA-IR, HDL cholesterol, triglyceride and pancreatic isoamylase. Odds ratios and 95%CI were estimated using the multiple logistic regression model with backward elimination. CI: Confidence interval; BMI: Body mass index; HOMA-IR: Homeostasis model assessment of insulin resistance.
no association with fasting and preload plasma glucose concentrations in the OGTT (Table 2). It is possible that pancreatic hyperechogenicity with insulin resistance precedes the development of diabetes in the non-diabetic general population. Thus, further large-scale prospective studies are necessary to investigate whether pancreatic hyperechogenicity is an early pathological event in the diabetes disease process.

Several recent studies have reported that hepatic steatosis and increased BMI are predictors of a hyper­echogenic pancreas[6,7]. In the present study, fatty liver was also significantly associated with pancreatic hyperechogenicity (OR = 1.77, 95%CI: 1.15-2.72, P = 0.009) (Table 2). Therefore, we performed additional analyses excluding participants with fatty liver in order to account for the effect of this condition in our results. The adjusted analysis showed that increased BMI, higher HOMA-IR score, and decreased adiponectin were also significantly associated with pancreatic hyperechogenicity (Table 4). This is the first study investigating the relationship between pancreatic hyperechogenicity and risk factors for metabolic syndrome by excluding the influence of fatty liver.

In this study, we used a simple and traditional method of assessing the severity of pancreatic hyperechogenicity, which was the comparison of echogenicity between the pancreatic body and the liver. However, this approach can potentially result in misdiagnosis of pancreatic hyperechogenicity if the extent of fatty liver is severe. We also performed additional analyses to exclude the influence of fatty liver. As shown in Tables 2 and 4, the results of our analyses that either included or excluded fatty liver, respectively, were similar and both showed increased BMI, higher HOMA-IR scores, and decreased adiponectin levels. However, our study had a limitation: No histological confirmation of pancreatic fat was possible.

There may be unknown factors that may cause the histological changes associated with obesity in addition to fat accumulation, fibrosis and functional changes in the exocrine pancreas. We recently demonstrated that intra-lobular fat accumulates in exocrine pancreatic tissue and that lipid droplets in acinar cells increase in Zucker diabetic fatty rats, which is an animal model of type 2 diabetes caused by the chronic intake of a high-fat diet. These conditions appear cause acinar cell injury and fibrosis. Thus, additional clinical and experimental studies of the interrelationships between diabetes, metabolic syndrome and pancreatic injury should be conducted to clarify the pathogenesis of “non-alcoholic fatty pancreatic disease”.

In conclusion, our study of a non-diabetic general population showed that pancreatic hyperechogenicity was independently associated with increased BMI, insulin resistance and hypoadiponectinemia.

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COMMENTS

Background

Pancreatic hyperechogenicity is thought to be related to the aging process. However, little is known about the association between pancreatic hyperechogenicity and other life-style related risk factors.

Research frontiers

Prior studies have reported that increased echogenicity of the pancreas is associated with pancreatic lipomatosis. Recent ultrasound studies have shown that pancreatic hyperechogenicity is correlated with obesity, hepatic steatosis, and insulin resistance.

Innovations and breakthroughs

This is the first study investigating the relationship between pancreatic hyperechogenicity and risk factors for metabolic syndrome by excluding the influence of fatty liver.

Applications

Pancreatic hyperechogenicity is independently associated with increased body mass index, insulin resistance, and hypoadiponectinemia in the general population. Pancreatic hyperechogenicity could be a useful marker of the metabolic syndrome.

Peer-review

Accept the manuscript for publication without significant corrections.

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