Regional and Overall Aortic Function In Nondiabetic Individuals With Insulin Resistance and Normal Glucose Tolerance

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Context: Insulin resistance is associated with altered vascular function in diabetes.

Objective: The objective of the study was to define the overall and regional aortic function as well as the changes of aortic function over time in nondiabetic individuals with insulin resistance and a normal oral glucose tolerance test (OGTT).

Design: This was a cross-sectional and longitudinal analysis with 12 months follow-up.

Setting: The setting of the study was in primary care.

Patients: Nondiabetic individuals (n = 181, mean age 42 ± 8 y) with a normal OGTT and insulin resistance as defined by the insulin sensitivity index (ISI) participated in the study.

Interventions: ISI was estimated from serial measurements of plasma insulin and glucose during an iv glucose tolerance test. Ascending and abdominal aortic distensibility (AoD) and stiffness index-β (AoSI) were assessed using echocardiography. Carotid-to-femoral artery pulse wave velocity (PWVc-f; an index of overall aortic function) was measured from carotid and femoral arteries Doppler flow velocities recorded simultaneously with an electrocardiogram. Associations between ISI, AoD, AoSI, and PWVc-f were assessed using linear regression analyses and ANOVA. Differences between baseline and 12 months were compared using a paired t test.

Main Outcome Measures: AoD and AoSI associations as well as changes over a 12-month period in relation to ISI were measured.

Results: Ascending AoD (P = .01) and ascending AoSI (P = .025) were significantly associated with ISI; in contrast, abdominal AoD and AoSI and PWVc-f did not. Changes in AoD, AoSI, and PWVc-f over time were more prominent in individuals with low ISI compared with those with high ISI.

Conclusions: The significant associations between ISI and aortic function suggest that insulin resistance may affect the cardiovascular system, even when OGTT is normal. (J Clin Endocrinol Metab 98: 4457–4463, 2013)

Stiff aorta is a predictor of cardiovascular events and mortality in patients with diabetes mellitus and in nondiabetic individuals (1, 2). Early detection of aortic stiffening and appropriate management may reduce or delay cardiovascular complications in patients with different diseases or apparently healthy individuals. Aortic function...
and thus stiff aorta can be estimated noninvasively by measuring aortic distensibility (AoD), aortic stiffness index (AoSf), or carotid-to-femoral artery pulse wave velocity (PWVc-f). AoD and AoSf can be assessed in the ascending and the abdominal aorta using echocardiographic techniques (3).

Abnormalities related to insulin sensitivity, plasma insulin concentrations, and glucose tolerance are observed prior to the development of type 2 diabetes mellitus in high-risk individuals, especially in those with a family history of type 2 diabetes mellitus (4–9). High insulin levels and insulin resistance may adversely affect the cardiovascular system and increase the cardiovascular risk, even in the prediabetic individuals (10–14). At this point, however, there are no studies to assess aortic function in prediabetic individuals with insulin resistance and a normal oral glucose tolerance test (OGTT) (15, 16).

It is known that the structure of the aortic wall and its blood supply differ between the ascending and the abdominal aorta. These differences in structure and blood supply between the thoracic and the abdominal aorta may result in different changes in regional aortic function in disease states and in individuals with insulin resistance. For early intervention, however, it is important to determine which part of the aorta is affected first.

The present study was undertaken to investigate the association between insulin resistance and regional (ascending and abdominal aorta) as well as overall aortic function in a well-defined group of individuals with decreased peripheral action of insulin and normal OGTT. Furthermore, because aortic dysfunction is progressive, changes in aortic function over a 12-month follow-up period were determined in relation to the degree of insulin resistance.

**Materials and Methods**

**Study population**

One hundred eighty-one (69 males, 112 females) nondiabetic African-Americans, mean age 42 ± 8 years, were studied. All subjects were the offspring of at least one parent with type 2 diabetes mellitus. Subjects were recruited from the Columbus, Ohio, area to prospectively investigate the effects of oral metformin, glipizide, or placebo on multiple cardiovascular parameters (17). In the present study, associations between insulin sensitivity and elastic properties of the aorta in the entire population (n = 181) were analyzed. For the follow-up analysis, only individuals in the placebo group (n = 97) were included because the other groups received an oral antidiabetic agent that may affect the results.

All individuals had a fasting plasma glucose of less than 110 mg/dL and a plasma glucose of less than 140 mg/dL 2 hours after the administration of a 75-g oral glucose load. The study protocol was initiated in the mid-1990s (first recruitment 1994). The normal plasma glucose at that time was considered to be less than 110 mg/dL and not less than 100 mg/dL, which was introduced by the American Diabetes Association in 2003. According to the study protocol, all individuals were at risk of developing type 2 diabetes mellitus and had decreased peripheral action of insulin as it was assessed by the insulin sensitivity index (ISI; see Metabolic studies). ISI was considered to be abnormal when the value of the ISI was at least 1 SD below the mean normal value [4.93 ± 0.46 × 10^{-4} min^{-1} (microunits per milliliter)^{-1}] for African-Americans without a family history of diabetes mellitus (18).

Individuals at baseline were divided into four quartiles according to ISI abnormality, which were ranged from mild (quartile 4) to severe (quartile 1) as follows: quartile 1 (n = 44), ISI less than 0.4 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}; quartile 2 (n = 44), ISI = 1.41–2.37 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}; quartile 3 (n = 47), ISI = 2.38–3.51 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}; and quartile 4 (n = 46), ISI = 3.52–4.47 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}. The median value of ISI of the individuals who have follow-up studies (n = 97) was 2.38 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}. This value was used to separate individuals in those with low [ISI ≤ 2.38 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}, n = 49] and those with high [ISI > 2.38 × 10^{-3} min^{-1} (microunits per milliliter)^{-1}, n = 48] ISI. Subjects with a history of liver, kidney, or heart diseases, pregnant or current breastfeeding women, and subjects on pharmacological agents with known effects on the cardiovascular system, glucose metabolism, or insulin levels were excluded prior to entry into the study. The protocol was approved by the Human Subjects Research Review Committee of The Ohio State University. Written informed consent was obtained from all individuals prior to enrollment into the study.

**Cardiovascular studies**

History and physical examination (body weight and height measurements were included) were performed in all individuals. Left ventricular (LV) mass was calculated using the following equation:

\[
LV	ext{ mass} = \frac{(1.04 \times [\text{SBP}] - 13.8 \times [\text{DBP}] + 3.4 \times [\text{LV mass index}] - 11.2 \times [\text{Pulse}] - 19.2 \times [\text{LV mass index}] - 11.2 \times [\text{Pulse}])}{100}
\]

\[
LV	ext{ mass index} = \frac{1}{100} \times (\text{LV mass} + 0.68 \times \text{LV mass index} + 0.68 \times \text{LV mass index})
\]

**Table 1. Baseline Characteristics of the Study Population (n = 181)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41 ± 7</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>69/112</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>123 ± 15</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79 ± 10</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>43 ± 11</td>
</tr>
<tr>
<td>LV mass index, g/m²</td>
<td>62 ± 14</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>80 ± 16</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>12.8 ± 7.3</td>
</tr>
<tr>
<td>Fasting C-peptide, ng/mL</td>
<td>2.7 ± 1.2</td>
</tr>
<tr>
<td>120-min glucose OGTT, mg/dL</td>
<td>94 ± 21</td>
</tr>
<tr>
<td>ISI, 10^{-3} min^{-1} (μU/mL)^{-1}</td>
<td>2.8 ± 1.6</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.55 ± 1.43</td>
</tr>
<tr>
<td>Hemoglobin A1c, mmol/mol</td>
<td>30.5 ± 9.4</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>182 ± 34</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49 ± 13</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>112 ± 32</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>86 (54–126)</td>
</tr>
</tbody>
</table>

Values are mean (SD); triglycerides are expressed as median (interquartile range). Abbreviations: A1c, glycosylated; DBP, diastolic BP; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M/F, males/females; SBP, systolic blood pressure.
formula: LV mass (grams) = 1.05 [(LV diastolic diameter + LV posterior wall diastolic thickness + interventricular septum diastolic thickness)^3 \times (LV diastolic diameter) - 13.6. LV mass was corrected for body surface area (BSA) (grams per square meter) to obtain the LV mass index (10).

Diameters of the ascending (3 cm above the aortic valve) and the abdominal aorta were measured in systole and diastole using echocardiographic techniques as described previously from our laboratory (3, 10, 17, 19–21).

The AoD was calculated using the following formula (3):

AoD (square centimeters \times \text{dynes}^{-10.10 \times 10^{-6}}) = 2 [(systolic aortic diameter) - (diastolic aortic diameter)/(diastolic aortic diameter)] \times pulse pressure, where pulse pressure = systolic blood pressure (BP) - diastolic BP.

The AoSI was calculated using the following formula (3):

AoSI = log n (systolic BP/diastolic BP)/[(systolic aortic diameter - diastolic aortic diameter)/(diastolic aortic diameter)].

The PWVc-f was measured from Doppler flow velocities of the carotid and femoral arteries, which were recorded simultaneously with the electrocardiogram. Times from the beginning of the QRS complex to the upstroke of the carotid artery Doppler flow velocity and from the beginning of the QRS complex to the upstroke of the femoral artery Doppler flow velocity were measured. PWVc-f was calculated as the ratio of the time required for the pulse wave to travel from the carotid to the femoral artery, over the distance between them (3, 10, 17, 19–21).

Figure 1. Whisker plots showing distensibility (AoD, upper panel) and stiffness index (lower panel) of the ascending aorta (Ao) at baseline according to the ISI quartiles (n = 181). Number of individuals in each quartile is shown.

The PWVc-f was measured from Doppler flow velocities of the carotid and femoral arteries, which were recorded simultaneously with the electrocardiogram. Times from the beginning of the QRS complex to the upstroke of the carotid artery Doppler flow velocity and from the beginning of the QRS complex to the upstroke of the femoral artery Doppler flow velocity were measured. PWVc-f was calculated as the ratio of the time required for the pulse wave to travel from the carotid to the femoral artery, over the distance between them (3, 10, 17, 19–21).

Metabolic studies

Two iv needles were inserted into the forearm veins while the subjects were in the supine position. One line was used to draw blood samples and the other for glucose and insulin administration.

The ISI was calculated from the serial measurements of plasma insulin and glucose levels during iv glucose tolerance test. Four blood samples were obtained at −20, −15, −10, and 0 minutes for basal plasma concentrations of glucose, C-peptide, and insulin. The average of the four measurements was taken as the baseline value. Thereafter, 0.3 g/kg glucose (in 50 mL of water) was infused over a 1-minute period. Nineteen minutes after the completion of glucose administration, 0.05 U/kg insulin (Humulin; Eli Lilly & Co), dissolved in 30 mL of 0.9% normal saline, was given iv over 60 seconds. Blood samples were obtained at frequent intervals from 2 to 180 minutes after insulin administration for plasma glucose, C-peptide, and insulin concentration assays. All samples were centrifuged at 4°C and the serum was frozen and stored at −20°C until assays were performed. The ISI was calculated using the minimal model software program (MINIMOD) described by Bergman et al (22). The ISI was considerate as a marker of peripheral (dynamic) insulin resistance.

Homeostasis model of assessment of insulin resistance (HOMA-IR) was calculated using the following formula:

fasting glucose (milligrams per deciliter)\times fasting insulin (microunits per milliliter)/405.

The OGTT was performed in all individuals prior to enrollment into the study. Each subject was instructed to ingest 250 g carbohydrate per meal in their regular meals for 3 consecutive days before the study. After a 10- to 12-hour overnight fast, all subjects ingested a 75-g oral glucose load (Kodalex) in a total volume of 250 mL over a 2-minute period. Blood samples for serum glucose, insulin, and C-peptide were obtained at baseline and at 30, 60, 90, and 120 minutes after the glucose administration. By protocol, all participants had plasma glucose of less than...
140 mg/dL 2 hours after the administration of 75 g oral glucose load (15).

Biochemical measurements

Plasma glucose concentrations were measured by the glucose oxidase method using a glucose autoanalyzer (Beckman). Insulin and C-peptide levels were determined by a standard double-antibody RIA technique at the Core Laboratory of The Ohio State University Medical Center. The sensitivity of the insulin assay was 2.5 μU/mL. The intra- and interassay coefficients of variation of insulin assay were 6% and 10%, respectively. The lower limit for the C-peptide assay was 0.47 ng/mL, and the intra- and interassay coefficients of variation were 7% and 13%, respectively. Lipid concentrations were measured in the Core Laboratory of The Ohio State University Medical Center (17).

Statistical analysis

Continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD and were compared using the Student’s t test. Nonnormally distributed data are expressed as median (interquartile range) and were compared using the Mann-Whitney U test. Quartiles of ISI were used to assess the associations between indices of aortic function and ISI at baseline (n = 181) using an ANOVA. Correlations were assessed with a Spearman’s correlation coefficient test. Multiple linear regression analyses were performed to identify significant independent associations between aortic function parameters and ISI adjusted for age, gender, heart rate, lipid profile, fasting glucose, and BSA. Differences between baseline and 12 months were compared using a paired Student’s t test. A value of P < .05 was considered to be statistically significant. All statistical analyses were performed using SPSS version 13 and JMPIN version 8 (SAS Institute).

Results

Demographic and clinical characteristics of the study population are presented in Table 1.

Elastic properties of the aorta (AoD, AoSI, PWVc-f) and ISI at baseline

AoD and AoSI of the ascending aorta were significantly related to ISI quartiles (ANOVA P = .01 and P = .025, respectively; Figure 1). After adjustment for significant confounders, both AoD and AoSI of the ascending aorta were still associated with ISI (t = 3.51, P = .005, and t = −2.82, P = .006, respectively). Similar results were obtained with HOMA-IR (ascending AoD, t = −3.25, P = .001; ascending AoSI, t = 2.58, P = .01). In linear regression analyses, weak but statistically significant correlations were found between ISI and AoD (r = 0.20, P = .003) and AoSI (r = 0.18, P = .035) for the ascending aorta (Supplemental Figures 1 and 2, published on The Endocrine Society’s Journals Online web site at http://jcem.endojournals.org). In contrast, abdominal AoD (P = .33), abdominal AoSI (P = .38), and PWVc-f (P = .77, an index of overall aortic function) were not related to ISI or HOMA-IR.

Changes of aortic function (AoD, AoSI, PWVc-f) during follow-up period: differences between baseline and 12 months in individuals with low and high ISI

Changes in cardiovascular parameters during the follow-up period were analyzed only in the placebo group of the initial study population (n = 97). Cardiovascular and metabolic parameters of individuals with high and low ISI are shown in Table 2. After 12 months of follow-up, individuals with low ISI (more insulin resistant, n = 49) showed a greater reduction in ascending AoD compared with those with high ISI (less insulin resistant, n = 48, Figure 2). Similarly, individuals with low ISI showed an increase in ascending AoSI, whereas individuals with high ISI did not (Figure 2). Abdominal AoD and AoSI did not change significantly over 12 months follow-up.

Likewise, PWVc-f, an index of overall aortic function, increased significantly only in the group with low ISI at 12 months (P = .01, Figure 3). It was a trend for LV mass to increase at 12 months in individuals with low ISI, but this did not reach statistically significant value (Figure 4). PWVc-f and LV mass index were significantly associated both at baseline (r = 0.30, P < .001, n = 181, Supplemental Figure 3) and at 12 months (r = 0.19, P < .01, n = 97).

Table 2. Metabolic and Cardiovascular Parameters in Individuals With Low and High ISI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low ISI (n = 49)</th>
<th>High ISI (n = 48)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>41 ± .7</td>
<td>40 ± .7</td>
<td>.23</td>
</tr>
<tr>
<td>Gender M/F</td>
<td>17/32</td>
<td>17/31</td>
<td>.89</td>
</tr>
<tr>
<td>BSA, m2</td>
<td>2.00 ± .2</td>
<td>1.9 ± .2</td>
<td>.04</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>125 ± 15</td>
<td>125 ± 15</td>
<td>.05</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82 ± 10</td>
<td>80 ± 11</td>
<td>.15</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>43 ± 11</td>
<td>41 ± 10</td>
<td>.21</td>
</tr>
<tr>
<td>LV mass index, g/m2</td>
<td>61.3 ± 15</td>
<td>61.7 ± 13</td>
<td>.69</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>83.5 ± 19.9</td>
<td>77.1 ± 12</td>
<td>.01</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>17.0 ± 7.5</td>
<td>8.6 ± 3.5</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Fasting C-peptide, ng/mL</td>
<td>3.2 ± 1.2</td>
<td>2.1 ± 1.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>120-min glucose OGGT, mg/dL</td>
<td>100.2 ± 20.7</td>
<td>91.1 ± 19.0</td>
<td>.0003</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>3.5 ± 1.3</td>
<td>1.9 ± 1.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hemoglobin A1c, mmol/mol</td>
<td>30.0 ± 9.3</td>
<td>26.8 ± 7.5</td>
<td>.04</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>180 ± 38</td>
<td>187 ± 30</td>
<td>.38</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>46.5 ± 13.0</td>
<td>51.0 ± 13.1</td>
<td>.02</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>108.1 ± 32</td>
<td>116 ± 25</td>
<td>.87</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>92 (58–131)</td>
<td>74 (46–97)</td>
<td>.007</td>
</tr>
</tbody>
</table>

Values are mean (SD); triglycerides are expressed as median (interquartile range). Abbreviations: A1c, glycosylated; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; M /F, males/females; SBP, systolic blood pressure.
This study demonstrated that in nondiabetic individuals with insulin resistance ranging from mild to severe, and normal OGTT ascending AoD and AoSI were associated with insulin resistance (ISI, HOMA-IR), whereas abdominal AoD and AoSI did not. Indices of aortic function were deteriorated in a short period of time (12 months) in individuals with more pronounced insulin resistance (low ISI), whereas these indices remained unchanged in individuals with a higher ISI. Furthermore, PWVc-f, an index of overall aortic function, was associated with ISI at the 12-month follow up. The data suggested a progressive involvement of the aorta in individuals with insulin resistance and normal OGTT.

The median value of ISI in this group was much lower than that reported previously from our laboratory in healthy African-Americans without a family history of type 2 diabetes mellitus \cite{4.93 \pm 0.46 \times 10^{-4}/min^{-1} (microunits per milliliter)^{-1}} \cite{18}. This value is even lower compared with white Americans of European descend \cite{7.17 \pm 0.88 \times 10^{-4}/min^{-1} (microunits per milliliter)^{-1}} \cite{18}.

Stiff aorta results in an increased in PWVc-f and reflected wave velocity. Increased PWVc-f will result in arteriolar and target organ damage,
and demonstrated that insulin resistance, assessed by ISI or 2 diabetic patients, extends experimental data to humans insulin resistance and normal OGTT, all offspring of type unique and well-defined population of individuals with type 2 diabetes mellitus. The present study, which used a stage of Otsuka Long-Evans Tokushima fatty rat model of tent and thickening of the aortic wall in the prediabetic over, Noma et al (29) found an increase of collagen con-
tent and thickening of the aortic wall in the prediabetic stage of Otsuka Long-Evans Tokushima fatty rat model of type 2 diabetes mellitus. The present study, which used a unique and well-defined population of individuals with insulin resistance and normal OGTT, all offspring of type 2 diabetic patients, extends experimental data to humans and demonstrated that insulin resistance, assessed by IS\textsubscript{A} or HOMA-IR, was independently associated with the elastic properties of the ascending aorta at the time during which OGTT was normal.

Furthermore, to determine which part of the aorta is affected first in individuals with insulin resistance and normal OGTT, distensibility and stiffness index of the ascending and abdominal aorta were measured separately. The reason(s) for this early involvement of the ascending aorta remain to be defined. An increase in adrenergic activity due to insulin resistance may result in alterations in especially in the kidneys and the brain. Increased reflected wave velocity will result in an increased of LV work and a decrease in the coronary blood flow. For these reasons, among others, stiff aorta is associated with increased cardiovascular morbidity and mortality in patients with different diseases and in apparently healthy individuals (1–3, 19, 23).

Impaired glucose uptake due to the resistance in the peripheral action of insulin is the fundamental pathophysiological abnormality in patients with type 2 diabetes mellitus. Insulin resistance, however, may be present for years prior to the onset of hyperglycemia. These individuals usually maintain normal fasting plasma glucose levels due to compensatory hyperinsulinemia but demonstrate varying degrees of glucose intolerance after a glucose load. It is known that high glucose concentrations induce vascular stiffening and aortic dysfunction (15, 16, 24–26). Experimental studies in insulin-resistant Zucker fa/fa rats, however, have shown that structural and molecular changes of the aortic wall, which were associated with stiff aorta, are present prior to the onset of hyperglycemia (27, 28). Moreover, Noma et al (29) found an increase of collagen content and thickening of the aortic wall in the prediabetic stage of Otsuka Long-Evans Tokushima fatty rat model of type 2 diabetes mellitus. The present study, which used a unique and well-defined population of individuals with insulin resistance and normal OGTT, all offspring of type 2 diabetic patients, extends experimental data to humans and demonstrated that insulin resistance, assessed by IS\textsubscript{A} or HOMA-IR, was independently associated with the elastic properties of the ascending aorta at the time during which OGTT was normal.

In conclusion, in nondiabetic African-Americans with insulin resistance, the elastic properties of the ascending aorta were affected first compared with the abdominal aorta and to overall aortic function. Deterioration of the elastic properties of the ascending aorta as well as in overall aortic function (increased PWV\textsubscript{c-f}) over time was observed in individuals with low, but not in those with high, IS\textsubscript{A}. Indices of aortic function may help to identify individuals with insulin resistance at risk for cardiovascular complications. Early detection and possible slowing of the vascular stiffening process with pharmacological agents and/or lifestyle interventions may reduce the associated risks for cardiovascular events in these individuals.
Acknowledgments

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References