Favorable Long-term Effect of a Low-Fat/High-Fiber Diet on Human Blood Coagulation and Fibrinolysis

Peter Marckmann, Brittmarie Sandström, and Jørgen Jespersen

In an 8-month strictly controlled dietary study of 16 healthy young men, the long-term effect of a low-fat (26% of energy) high-fiber (4.5 g/MJ) diet on cardiovascular risk markers of the hemostatic system was assessed. Fasting blood sampling was performed during a 4-week baseline period and then monthly during the intervention. A matched control group of 16 men on habitual diets was also monitored. Median fibrinolytic activity of tissue-type plasminogen activator (t-PA) in plasma was significantly elevated (twofold to fourfold) by the experimental diet. A significant increase in the systemic fibrinolytic activity of the euglobulin fraction of plasma was also observed. Median plasma factor VII coagulant activity (F VIIc) was depressed by 5–10% during the first 2 months and the last month of the study period. The dietary change did not significantly affect plasma levels of fibrinogen, t-PA antigen, or plasminogen activator inhibitor type 1 antigen. In conclusion, young men who were switched from a typical Danish diet high in saturated fat to a low-fat/high-fiber diet showed a permanent increase in plasma fibrinolytic activity and a biphasic decrease in F VIIc. The dietary change thus had a favorable effect on cardiovascular risk markers of the hemostatic system. (Arteriosclerosis and Thrombosis 1993;13:505–511)

KEY WORDS • factor VII • fibrinogen • tissue-type plasminogen activator • plasminogen activator inhibitor type 1 • diet intervention • cardiovascular risk

The complex and interacting biological processes of coagulation and fibrinolysis control the formation and resolution of fibrin in the human body. Fibrin is an essential component of the proliferative lesions of atherosclerosis and intravascular thrombi. It is therefore tempting to assume that changes in the coagulant and/or fibrinolytic activity may affect the risk of atherogenesis and thrombogenesis. This view is supported by the observation that hemostatic variables may act as independent risk markers of subsequent events of ischemic heart disease.

Short-term studies have indicated that coagulation and fibrinolysis may be influenced by dietary modifications and that low-fat/high-fiber diets may cause favorable changes in these systems. In the present study, we investigated whether a low-fat/high-fiber diet might influence coagulation and fibrinolysis over a longer time period. The study was a strictly controlled dietary study of 16 young men and lasted 8 months.

Methods

The study design has been described in detail elsewhere. Thirty-two healthy male students with typical Danish dietary habits as assessed from a dietary history interview were selected for the present study and were assigned to either an experimental group (n=16) or a control group (n=16). After a 4-week period of baseline examinations and blood sampling, the experimental group initiated a 245-day (8-month) intervention period of a strictly controlled experimental diet. The individuals of the control group were asked to keep their diet and lifestyle unchanged. Five individuals in each group were smokers (three light [<5 cigarettes per day] and two moderate [<15 cigarettes per day] smokers in each group).

All participants were advised of the protocol at the initiation of the study, and informed consent was obtained. The trial was approved by the Medical Ethics Committee of Frederiksberg, Denmark.

Diet

The habitual diet of the experimental group was assessed from 7-day weighed-food records during the baseline period (Table 1). The dietary habits of the control subjects were monitored by repeated (three) 7-day weighed-food records during the trial period and showed no changes (Table 1). All food records were validated by analysis of 24-hour urinary excretion of nitrogen as described.

The experimental diet was an implementation of the Nordic Nutrition Recommendations, i.e., a low-fat/high-fiber diet. It consisted of a carefully planned,
Blood Sampling and Analysis

Blood was drawn with minimal stasis from an antecubital vein. Samples were collected in the morning (between 8 and 10 AM) after 20 minutes of supine rest. The participants had fasted (≥12 hours) and had abstained from alcohol for 24 hours, from heavy physical activity for 36 hours, and from any kind of drugs, including aspirin, for 48 hours. Study holidays were not allowed in the week preceding blood sampling. Silicoconized, evacuated tubes and 20-gauge needles were used.

28-day recycling menu of three main meals and one snack per day and was prepared in the metabolic kitchen of the department. A combination of fixed amounts of fat-containing foods according to estimated energy requirements and voluntary choices of low-fat food items from the menu was used to control the fat intake and at the same time to allow for fluctuations in appetite. The voluntary intake was individually recorded by a computerized balance. Lunch and dinner were eaten at the department during weekdays, whereas prepacked breakfasts, snacks, and weekend meals were supplied to be eaten at home. The experimental diet accounted for approximately 80% (range, 67–92%) of total energy intake of the participants during the 8 months of the trial. The self-selected and recorded consumption of snacks and occasional single meals accounted for an additional 10% (range, 1–23%) of total energy intake. On average, the 20 unrecorded "study holidays" (compare with the total duration of the study, which lasted 245 days) were estimated to account for the last 10% (range, 8–13%) of total energy intake. The interindividual differences in dietary compliance were not associated with significant differences in biological responses.

The calculated nutrient composition of the total dietary intake during the intervention period, study holidays excluded, is presented in Table 1.

**Table 1. Calculated Daily Energy and Nutrient Content of Habitual Diets of Control and Experimental Groups and of Dietary Intake During Intervention**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group (n=16)</th>
<th>Experimental group (n=16)</th>
<th>Dietary intake during intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MJ</td>
<td>12.6±2.2</td>
<td>13.8±3.0</td>
<td>14.4±1.6</td>
</tr>
<tr>
<td>kcal</td>
<td>3,014±526</td>
<td>3,301±718</td>
<td>3,445±383</td>
</tr>
<tr>
<td>From protein (%)</td>
<td>13.9±1.8</td>
<td>13.5±1.3</td>
<td>13.9±0.9</td>
</tr>
<tr>
<td>From fat (%)</td>
<td>35.1±4.4</td>
<td>36.8±4.1</td>
<td>25.7±0.9</td>
</tr>
<tr>
<td>From carbohydrates</td>
<td>46.7±5.9</td>
<td>44.9±4.8</td>
<td>58.0±1.7</td>
</tr>
<tr>
<td>From alcohol (%)</td>
<td>4.4±3.2</td>
<td>4.9±3.7</td>
<td>2.1±1.2</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>100±17</td>
<td>109±23</td>
<td>118±16</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>115±23</td>
<td>134±33</td>
<td>97±11</td>
</tr>
<tr>
<td>SFAs (g)</td>
<td>46.10</td>
<td>51±16</td>
<td>32±4</td>
</tr>
<tr>
<td>PUFAs (g)</td>
<td>17.5</td>
<td>21±7</td>
<td>24±3</td>
</tr>
<tr>
<td>PUFAs/SFAs</td>
<td>0.38±0.13</td>
<td>0.43±0.12</td>
<td>0.77±0.06</td>
</tr>
<tr>
<td>Carbohydrates (g)</td>
<td>346±86</td>
<td>362±92</td>
<td>491±57</td>
</tr>
<tr>
<td>Dietary fiber (g)</td>
<td>28±7</td>
<td>33±12</td>
<td>56±9</td>
</tr>
</tbody>
</table>

SFAs, saturated fatty acids; PUFAs, polyunsaturated fatty acids. Values are mean±SD.

*The Danish food composition tables 1989 were used for the calculations. The description of habitual diets was based on one 7-day food record from each individual.

The first 10 mL of blood was collected in tubes without additives for lipid analysis (results presented in detail elsewhere). Subsequently, we collected 5 mL in a citrated tube (Vacutainer 606608, Becton Dickinson, Meylan-Cedex, France) for factor VII activity (F VIIc) and fibrinogen analysis and 2×5 mL in precooled citrated tubes (Vacutainer 606608) for fibrinolytic assays. After 10 minutes of venous occlusion of the opposite arm at diastolic pressure plus 10 mm Hg, an additional 5 mL was collected in precooled citrated tubes for fibrinolytic assays. All samples were spun for 15 minutes at 3,000g. The precooled tubes were spun at 1°C and the others at 20°C. The separated plasma was pipetted into plastic vials, then rapidly frozen at −50°C within 2 hours, and stored at −80°C. Analysis was performed in one series for each participant after completion of the study.

Plasma F VIIc (percent) was measured in a one-stage clotting assay, clottable fibrinogen (in micromoles per liter) was determined by a modified Clauss assay, and euglobulin and tissue-type plasminogen activator fibrinolytic activities (EFA and t-PA activity, respectively) (in milli–international units per milliliter) were assessed on fibrin plates as previously described. The total plasma antigen concentrations (in nanograms per milliliter) of t-PA and plasminogen activator inhibitor type 1 (PAI-1) were determined by enzyme-linked immunosorbent assay methods (Biopool Imulyse 5 t-PA and TintElize PAI-1; Biopool, Umeå, Sweden). Plasma PAI activity was determined by an amidolytic assay and expressed as the number of international units of t-PA per milliliter. There was a close correlation between PAI-1 antigen and PAI activity (see "Results"), suggesting the absence of significant in vitro release of PAI-1 from platelets. Serum total cholesterol, high density lipoprotein cholesterol, and triglyceride concentrations were determined by enzymatic methods (Boehringer-Mannheim GmbH, Mannheim, FRG).
TABLE 2. Anthropometric Characteristics, Blood Lipids, and Hemostatic Variables of the Experimental and Control Groups at Study Entry

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental (n=16)</th>
<th>Control (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24 (20–28)</td>
<td>24 (21–29)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.7 (50.4–84.6)</td>
<td>70.0 (63.8–80.9)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.82 (1.67–1.88)</td>
<td>1.85 (1.77–1.90)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.3 (17.2–26.7)</td>
<td>20.8 (19.4–24.5)</td>
</tr>
<tr>
<td>S–total cholesterol (mmol/L)</td>
<td>4.33 (3.41–5.81)</td>
<td>4.29 (2.89–5.86)</td>
</tr>
<tr>
<td>S–HDL cholesterol (mmol/L)</td>
<td>1.13 (0.94–1.67)</td>
<td>1.17 (0.81–1.60)</td>
</tr>
<tr>
<td>S–triglycerides (mmol/L)</td>
<td>0.68 (0.47–1.47)</td>
<td>0.82 (0.55–1.52)</td>
</tr>
<tr>
<td>P–F VIIc (%)</td>
<td>93 (67–128)</td>
<td>100 (57–123)</td>
</tr>
<tr>
<td>P–fibrinogen (μmol/L)</td>
<td>6.0 (4.2–9.6)</td>
<td>6.5 (5.5–10.0)</td>
</tr>
<tr>
<td>P–EFA (mIU/mL)</td>
<td>750 (344–1,480)</td>
<td>577 (234–1,678)</td>
</tr>
<tr>
<td>P–t-PA activity (mIU/mL)</td>
<td>94 (0–431)</td>
<td>93 (0–675)</td>
</tr>
<tr>
<td>P–t-PA antigen (ng/mL) (after venous occlusion)</td>
<td>3.1 (0.4–5.6)</td>
<td>3.7 (2.0–5.9)†</td>
</tr>
<tr>
<td>P–t-PA antigen (ng/mL)</td>
<td>11.8 (4.0–24.2)</td>
<td>9.5 (4.8–16.4)</td>
</tr>
<tr>
<td>P–PAI-1 antigen (ng/mL)</td>
<td>4.9 (0.5–10.3)</td>
<td>4.7 (1.6–34.6)</td>
</tr>
<tr>
<td>P–PAI activity*</td>
<td>4.5 (0.0–12.9)</td>
<td>4.1 (1.3–13.8)</td>
</tr>
</tbody>
</table>

S, serum; HDL, high density lipoprotein; P, plasma; F VIIc, factor VII activity; EFA, euglobulin fibrinolytic activity; t-PA, tissue-type plasminogen activator; PAI-1, plasminogen activator inhibitor type
1. Values are median and (range).
* n=8 from each group.
†Mann-Whitney U test: p<0.05.

Results

There were no significant differences at study entry between the experimental and the control group with regard to age; weight; height; body mass index; or serum concentrations of total cholesterol, high density lipoprotein cholesterol, or triglycerides. The plasma levels of t-PA antigen were lower in the experimental group (p<0.05), whereas no significant differences were observed for baseline levels of F VIIc, fibrinogen, EFA, t-PA activity, t-PA antigen after venous occlusion, PAI-1 antigen, or PAI activity (Table 2).

F VIIc changed significantly in the experimental group (Friedman statistics, p<0.0001; Table 3 and Figure 1). A biphasic response to the experimental diet was seen with initial and final depressions of F VIIc (days 28, 56, and 245). Midperiod samples (days 77, 140, and 196) did not differ from baseline. The control group showed no changes (Friedman statistics, p=0.75; Table 4).

Fibrinogen levels remained unchanged during intervention (Friedman statistics, p=0.45; Table 3). The control group also showed no significant changes with time (Friedman statistics, p=0.60).

Systemic fibrinolytic activity. Median plasma t-PA activity was significantly influenced by the experimental diet (Friedman statistics, p<0.008; Table 3 and Figure 2). An almost fourfold increase was observed after the first 2 months of intervention. Subsequently a small and gradual decline occurred, so that on day 245 the median was 2.7 times higher than the baseline value. Concomitantly, the median EFA doubled after dietary intervention. Here again an initial sharp rise was followed by a slight leveling off (Table 3 and Figure 2). The control group showed no significant trends with time for either t-PA activity or EFA (Friedman statistics, p=0.53 and 0.37, respectively; Table 4).

Blood samples were obtained weekly from the experimental group during the baseline period (days -28 to 0). The fourth sample was used for baseline assessment of F VIIc, fibrinogen, fibrinolytic variables, and blood lipids. Subsequently, blood was sampled on days 56, 77, 140, and 245 for analysis of fibrinogen and fibrinolytic variables and on days 28, 56, 77, 140, 196, and 245 for F VIIc and lipid determinations. The control subjects had blood taken for F VIIc and lipid analysis at their first visit (day 14) and on days 42, 70, 133, 161, 203, and 238, whereas blood for fibrinogen and fibrinolytic variables was drawn only on days 42, 70, 161, and 203. A less frequent sampling of blood for fibrinogen and fibrinolytic variables had to be chosen for practical reasons. Furthermore, blood for fibrinolytic assays was not sampled at first visits to eliminate the systematic error introduced by first-visit anxiety.15

Statistics

Because of skewed distributions of most variables, nonparametric statistics were applied. Baseline measurements of the experimental group and first-time measurements of the control group were compared by the Mann-Whitney U test. The effect of time was assessed by the Friedman two-way analysis of variance for the experimental and control groups. The Wilcoxon matched-pairs signed-rank test was used to compare initial measurements with measurements at any later occasion whenever a significant effect of time was demonstrated. Correlation analysis was performed with Spearman statistics.16 A significance limit of 0.05 was chosen. Confidence intervals (90%) of the median were estimated by nonparametric statistics.17 All computations were performed using the spss/rc+ statistical package (SPSS Inc., Chicago).
Plasma t-PA antigen tended to decrease in the experimental group (Friedman statistics, \( p = 0.08 \); Table 3). No such trend was noted in the control group (Friedman statistics, \( p = 0.32 \)). The two groups had similar and constant values of t-PA antigen after venous occlusion (Friedman statistics, \( p = 0.25 \) for both groups).

Plasma PAI-1 antigen concentrations did not change significantly in either the experimental or the control group (Friedman statistics, \( p = 0.67 \) and 0.78, respectively).

Plasma PAI activity was measured in a random subsample of eight individuals from each group. No significant changes were observed (Friedman statistics, \( p = 0.63 \) and 0.47, experimental and control groups, respectively). In both groups and on all sampling occasions, PAI activity levels were closely associated with PAI-1 antigen concentrations, with Spearman's correlation coefficient \( r_s \) varying from 0.77 to 0.97 and probability values from 0.03 to less than 0.0001. The only insignificant association was seen in the last sample from the control group, in which case \( r_s = 0.67 \) and \( p = 0.07 \).

Blood lipids. Serum total and high density lipoprotein cholesterol decreased significantly during the first month of intervention and stayed at these lower levels throughout the intervention period as described\(^{10} \) (Table 3). Serum triglyceride levels did not change during intervention. No significant changes were noted among the control group.

Body weight. In the intervention group, mean body weight was 1.4 kg lower than initial values midway in the study, but at the end of the study it did not differ from initial mean body weight.\(^{10} \) The control subjects did not have a change in body weight.

Correlation analysis of individual changes from day 0 to day 56 was performed for the experimental group.
Plasma PAI-1 antigen changes correlated negatively with changes in EFA \((r_s = -0.51, p = 0.04)\) and positively with changes in t-PA antigen levels \((r_s = 0.61, p = 0.01)\) and tended to be associated with triglyceride changes \((r_s = 0.44, p = 0.09)\). Changes in t-PA activity and EFA were strongly associated \((r_s = 0.80, p = 0.0002)\). There were no significant associations between changes in plasma t-PA antigen levels and t-PA activity or EFA, or between changes in hemostatic variables and blood lipids.

**Discussion**

With regard to the primary prevention of ischemic heart disease, it is very important to know the long-term effect of a dietary change on the cardiovascular risk profile of healthy individuals. Dietary intervention trials of more than a few weeks' duration are, however, scarce and with few exceptions, 18, 19 have primarily included individuals at risk for arterial disease. 20-22 Furthermore, none of the studies of low-risk groups have investigated the dietary influence on coagulation and fibrinolysis.

We expected the experimental diet to cause a depression of fasting plasma F VIIc (and F VII protein) levels according to our earlier observations of individuals fed a comparable diet for 2 weeks. 8 A depressed F VIIc level was also seen on days 28 and 56 of intervention, but on days 77-196 it was not significantly different from initial values. On the last sampling occasion (day 245), F VIIc was again low. It is possible that these findings reflect the fact that 95% of the (on average) 20 study holidays on which the dietary intakes were unknown to us were placed between days 85 and 210. This would mean that a low-fat/high-fiber diet may lower fasting plasma levels of F VIIc only so long as it is strictly followed and that deviations from such a diet are rapidly reflected in F VIIc. The mechanism by which a low-fat/high-fiber diet may influence F VIIc is not known, but it has been suggested that triglyceride-rich lipoproteins might affect either the extent of F VII activation or F VII protein catabolism. 23 In our study the participants showed no changes in fasting triglyceride levels compared with baseline values. However, this does not exclude the possibility that triglyceride-rich lipoproteins could explain the observed F VIIc changes, since the postprandial flux of triglyceride-rich lipoproteins on the low-fat, experimental diet must have differed from that seen on the habitual high-fat diet.

Plasma fibrinogen was unaffected by the dietary change to a low-fat/high-fiber diet. This is in good agreement with our observations from controlled dietary trials of shorter duration. 9, 24 Others have reported that the daily intake of 14 g fish oil concentrate (approximately 7 g eicosapentaenoic and docosahexaenoic acids) may lower fibrinogen levels and have proposed that this effect is caused by the long-chain n-3 fatty acids of the fish oil, 25 but this finding is equivocal. 26 In the present study, the participants' daily intakes of fish (63 g) and marine n-3 fatty acids (approximately 1 g) were doubled compared with habitual intakes without causing changes in fibrinogen levels. Therefore, if n-3 fatty acids influence fibrinogen levels, they may only do so with high intakes—intakes much higher than could be reached by eating fish.

A prominent finding of the present trial was the substantial and sustained increase of the plasma EFA

**TABLE 4. Hemostatic Variables of the Control Group (n=16)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>14</th>
<th>42</th>
<th>70</th>
<th>133</th>
<th>161</th>
<th>203</th>
<th>238</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-F VIIc (%)</td>
<td>100</td>
<td>95</td>
<td>93</td>
<td>102</td>
<td>107</td>
<td>100</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>57-123</td>
<td>72-140</td>
<td>81-206</td>
<td>74-148</td>
<td>74-164</td>
<td>69-149</td>
<td>72-169</td>
<td>0.75</td>
</tr>
<tr>
<td>P-EFA (mIU/mL)</td>
<td>...</td>
<td>577</td>
<td>546</td>
<td>...</td>
<td>617</td>
<td>624</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>224-1,678</td>
<td>0-1,698</td>
<td>251-2,025</td>
<td>234-1,369</td>
<td></td>
<td></td>
<td></td>
<td>0.37</td>
</tr>
<tr>
<td>P-t-PA (mIU/mL)</td>
<td>...</td>
<td>93</td>
<td>66</td>
<td>...</td>
<td>72</td>
<td>103</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0-675</td>
<td>0-682</td>
<td>0-803</td>
<td>0-387</td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
</tbody>
</table>

P, plasma; F VIIc, factor VII activity; EFA, euglobulin fibrinolytic activity; t-PA, tissue-type plasminogen activator. Values are median and range. *Friedman two-way analysis of variance.
and t-PA fibrinolytic activity throughout the 8-month-long study period. A dietary influence on fibrinolysis has also been reported from trials of hyperlipemic or obese patients.\textsuperscript{7,21,22} In these trials, a lowering of serum triglyceride level was seen in parallel with a change in fibrinolysis, and these changes were considered interrelated. However, in our study the sharp rise in systemic fibrinolytic capacity was not accompanied by triglyceride changes. Furthermore, t-PA activity and EFA changes were not associated with any other blood lipid changes. Thus, dietary changes may favorably influence blood fibrinolysis without affecting blood lipids. This is a confirmation of our earlier findings.\textsuperscript{9}

The increase in systemic fibrinolytic activity occurred despite unchanged plasma levels of t-PA and PAI-1 antigen. This might seem to be a paradox, since t-PA and PAI-1 are considered the most important regulators of plasma fibrinolytic capacity. However, in young and healthy individuals the intraindividual variability of plasma t-PA and PAI-1 antigen is very large.\textsuperscript{27} Thus, our statistical power to detect changes of 20% in t-PA and PAI-1 antigen was less than 65%. Therefore, we could have easily overlooked explanatory changes in these variables in our study. Furthermore, the observed changes in EFA were indeed significantly and inversely associated with changes in plasma PAI-1 levels. The possibility that our finding was an artifact due to differential precipitation of t-PA and PAI-1 in the euglobulin fraction of plasma in response to blood lipid changes was excluded by supplementary analytical studies. Whether changes in other components of the complex fibrinolytic system might have contributed to the findings remains to be clarified.

The participants of our study made a complex dietary change from the habitual to the experimental situation. Thus, it is not possible to identify any specific nutrient(s) responsible for the observed effects on plasma F VIIc and fibrinolytic activity. Others have proposed that the dietary fat content may be important,\textsuperscript{6} but we were unable to demonstrate any effect on coagulation and fibrinolysis in a controlled trial comparing diets differing only in fat contents.\textsuperscript{28} From a cross-sectional epidemiological study, it has been suggested that a high consumption of fruits, vegetables, and root vegetables may increase the activity of the fibrinolytic system.\textsuperscript{28} If this can be confirmed, it could partly explain our findings. However, experimental evidence for that hypothesis is still lacking.

In conclusion, our study has shown that a shift from a typical Danish diet to a low-fat/high-fiber diet may affect coagulation and fibrinolysis in healthy young men. The experimental diet had the ability to lower F VIIc and fibrinolytic activity. These variables have been identified as prognostic markers of ischemic heart disease.\textsuperscript{2,4,5} We have reported earlier on the beneficial effects of the same experimental diet on blood lipids, systolic blood pressure, and body weight.\textsuperscript{10} Thus, a low-fat/high-fiber diet may, in a multifaceted way, favorably affect the cardiovascular risk profile of healthy individuals. Our results are in good agreement with and may explain the findings in a recently published clinical trial of postinfarct patients, in whom a comparable diet was shown to reduce the number of recurrent coronary thromboses after 1 year.\textsuperscript{29}

Acknowledgments

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References

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