routine analysis. Moreover, the high glucose concentrations observed in 11 patients made it impossible to quantify trimethylamine N-oxide and some other metabolites, including glycine (3.57 ppm) and betaine (3.27 ppm), consistently present in the controls, because of the overlap of their respective peaks with the glucose signals.

The ratios of metabolites to creatinine in the nondiabetic children and adolescents were generally comparable to those reported earlier in healthy adults (3), but that of acetate was significantly higher in the Finnish children than in the Italian adults (37.1 ± 5.5 vs 8.3 ± 1.3 mmol/mol of creatinine; \( P < 0.001 \)). The metabolites were also analyzed as a function of age based on the three age groups established. No significant differences were observed among the age groups, except for citrate, which decreased significantly with age (\( P = 0.03 \)), being 254 ± 34 mmol/mol of creatinine in the youngest (<10 years) age group, 209 ± 29 mmol/mol of creatinine in the children 10–14 years of age, and 113 ± 15 mmol/mol of creatinine in children >14 years. In contrast, there were no differences in urinary citrate in relation to age. Significant differences were observed in several metabolites between the patients and the age- and sex-matched controls. Highly significant differences were seen for citrate, alanine, lactate, and hippurate, which were all higher in diabetic children than in the unaffected individuals (Table 1). Urinary lactate (\( P < 0.01 \)) and acetate (\( P < 0.03 \)) were increased in the patients with poor metabolic control (HbA1c >8.0%) in comparison with patients with good metabolic control (HbA1c <8.0%). No differences were observed for the other metabolites in relation to HbA1c, although a wider range was characteristic of the patients with impaired metabolic control.

Alanine, lactate, acetate, and citrate were significantly

![Fig. 1. Typical 1H NMR spectral profiles of urine samples from a type 1 diabetes patient (A) and from a healthy control (B).](https://academic.oup.com/clinchem/article-abstract/48/4/660/5641657)
Furthermore, citrate reabsorption is mainly sensitive to the effect of glucosuria on the citrate transport carrier, suggesting that the increase of citrate may be mainly related in those patients with HbA1c diabetes. High hippurate excretion may reflect an adequate acid excretion rate (8), and a reduced concentration of hippurate indicates a reduced ability of the kidney to eliminate acids and may hence be considered an early marker of impaired renal function.

The ability of NMR spectroscopy to detect all three ketone bodies provides simultaneous information on their specific relationships. Further information on metabolic status was obtained by assessing acetate concentration, which was higher in patients with HbA1c >10.0% and with glucosuria >180 mmol/L, i.e., in patients with inadequate metabolic control.

In conclusion, NMR spectroscopy may provide a relevant method for the study of metabolites that could be useful markers in monitoring metabolic status and renal function in patients with type 1 diabetes. Such metabolites are not readily measurable with traditional techniques.

This work was supported Grants 98.03087.CT04 and 99.02529.CT04 from the Italian National Research Council (C.N.R.). We thank Salme Leskelä for help in collection of the samples.

### References

### Table 1. NMR results for urine samples from children with type 1 diabetes (n = 25) and age- and sex-matched controls (n = 25).

| Metabolite | Controls Mean | Type 1 diabetes Mean | SD | SE | Mean | SE | P
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Citrate</td>
<td>217.4</td>
<td>406.0</td>
<td>24.2</td>
<td>28.8</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TMAO(^b)</td>
<td>62.7</td>
<td>ND</td>
<td>10.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine</td>
<td>50.6</td>
<td>104.7</td>
<td>4.7</td>
<td>10.4</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lactate</td>
<td>39.6</td>
<td>150.1</td>
<td>6.6</td>
<td>28.8</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hippurate</td>
<td>311.3</td>
<td>555.5</td>
<td>42.2</td>
<td>80.9</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acetate</td>
<td>37.1</td>
<td>32.5</td>
<td>5.5</td>
<td>1.3</td>
<td></td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

\(^a\) Results are expressed as mmol/L of creatinine.

\(^b\) TMAO, trimethylamine Oxide; ND, not determined; NS, not significant.

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**Nanotechnology and Applications: An All-Language Literature Survey Including Books and Patents, Larry J. Kricka** and **Paolo Fortina**

(1) Department of Pathology and Laboratory Medicine, University of Pennsylvania Medical Center, 3400 Spruce St., Philadelphia, PA 19104; (2) The Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine, 310-C Abramson Pediatric Research Center, 34th St. and Civic Center Blvd., Philadelphia, PA 19104; author for correspondence: fax 215-662-7529, e-mail kricka@mail.med.upenn.edu

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