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# Cerebrospinal fluid to serum glucose ratio in non-hypoglycorrhachic neurological conditions

## 在非腦脊液糖份過少的神經狀況下腦脊液與血清葡萄糖之比率

**Objective.** To explore the relevance of cerebrospinal fluid to serum glucose ratio in non-hypoglycorrhachic conditions.

**Design.** Retrospective observational study.

**Setting.** Neurology ward, university teaching hospital, Hong Kong.

**Patients.** Adult patients with conditions unrelated to hypoglycorrhachia who underwent lumbar puncture.

**Main outcome measures.** Cerebrospinal fluid and simultaneous serum glucose concentrations, and their ratio to each other.

**Results.** Between September 1998 and August 2003, 170 cerebrospinal fluid and serum glucose samples were collected from 138 patients. Mean cerebrospinal fluid to serum glucose ratio was 0.61 (standard deviation, 0.142; range, 0.21-1.00). With the exception of cerebrospinal fluid protein level, laboratory parameters were similar among different diseases. The glucose ratio was lower than 0.6 in 43% and lower than 0.5 in 19% of samples. Cases with a low glucose ratio appeared to have higher serum glucose concentrations (significant among groups with different glucose ratios,  $P < 0.001$ ). The mean glucose ratio (0.65) was also significantly higher in patients with serum glucose concentration of lower than 7.8 mmol/L compared with those with serum glucose concentration between 7.8 and 11.1 mmol/L (mean, 0.46), or higher than 11.1 mmol/L (mean, 0.46) [ $P < 0.001$ ]. There was a strong negative correlation between the glucose ratio and serum glucose concentration ( $r = -0.704$ ,  $P < 0.001$ ).

**Conclusion.** A lowered cerebrospinal fluid to serum glucose ratio is often seen in the absence of an appropriate disorder, especially when simultaneous serum glucose concentration is elevated. This may be explained by the saturation kinetics of glucose transportation in hyperglycaemia, and the time lag for cerebrospinal fluid and glucose to equilibrate when the blood level fluctuates.

### Key words:

Blood glucose;  
 Cerebrospinal fluid;  
 Glucose/cerebrospinal fluid;  
 Spinal puncture

### 關鍵詞：

血糖；  
 腦脊液；  
 葡萄糖／腦脊液；  
 脊椎穿刺

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**目的：**探究在非腦脊液糖份過少的神經狀況下，腦脊液與血清葡萄糖比率的相關性。

**設計：**回顧性觀察研究。

**安排：**香港一所大學教學醫院的神經病學病房。

**患者：**從腰椎被抽取腦脊液的成年患者，其發病不會引致腦脊液糖份過少。

**主要結果測量：**腦脊液與血清葡萄糖濃度及兩者的比率。

**結果：**在1998年9月至2003年8月間，從138位病者中收集了170份腦脊液及血清葡萄糖的樣本。他們腦脊液與血清葡萄糖比率的平均數是0.61（標準差，0.142；範圍，0.21-1.00）。除了腦脊液蛋白質水平外，其餘參數在不同疾病組別間大致接近。43%的樣本葡萄糖比率少於0.6；19%的葡

葡萄糖比率少於 0.5。低葡萄糖比率個案出現血清葡萄糖濃度較高的情況（此情況在多個不同葡萄糖比率組別中是顯著的， $P < 0.001$ ）。與血清葡萄糖為 7.8 至 11.1 mmol/L（葡萄糖平均比率為 0.46）或高於 11.1 mmol/L（平均數為 0.46）的患者比較，血清葡萄糖少於 7.8 mmol/L 的患者的葡萄糖比率平均數（0.65）顯著較高（ $P < 0.001$ ）。葡萄糖比率與血清葡萄糖濃度成強烈反比關係（ $r = -0.704$ ,  $P < 0.001$ ）。

**結論：**腦脊液與血清葡萄糖比率降低經常出現在無病變的患者身上，尤其在血清葡萄糖同時提高的情況下。此現象可能是因為高血糖症患者的葡萄糖轉化動力飽和，及血液水平波動時，腦脊液與葡萄糖達至均衡時出現的時間滯差所致。

## Introduction

Lumbar puncture (LP) is an important and frequently performed procedure. The nature of an underlying pathology is often reflected by changes in cerebrospinal fluid (CSF) constituents. Low glucose concentration, or hypoglycorrhachia, indicates the presence of diffuse meningeal disorders, such as bacterial, fungal, or tuberculous infection, leptomeningeal carcinomatosis, other aseptic meningitides, and subarachnoid haemorrhage.<sup>1-3</sup> Most of these conditions are life-threatening and must be promptly diagnosed and treated. Normal CSF glucose concentration ranges from 2.5 to 4.5 mmol/L.<sup>1</sup>

There is a dynamic equilibrium between blood and CSF glucose levels; fluctuations in blood glucose parallel changes in the CSF.<sup>1,4</sup> Hypoglycorrhachia can be masked by hyperglycaemia, and lowered CSF glucose during hypoglycaemia may be misinterpreted as meningitis. This misleading effect can be corrected by estimating the CSF to blood glucose ratio, which derives a fairly constant value. The widely accepted normal ratio is between 0.6 and 0.8, although 0.5 has also been considered the lower limit of normal.<sup>1,3,5-7</sup> Less than this level indicates pathological hypoglycorrhachia.

The concept of a 'normal' ratio had been challenged as an over-simplification of the relationship between CSF and serum glucose at different concentrations.<sup>8,9</sup> A study of 79 men with no CSF abnormalities and the published data from about 100 normal subjects revealed that the CSF to blood glucose ratio was not a valid measure of their true relationship.<sup>9</sup> In addition, previous reports often focused on healthy subjects or excluded those with abnormal CSF findings. This study aimed to explore the relevance of CSF to serum glucose ratio in patients with neurological disorders.

## Methods

The admission and follow-up records of patients who had CSF collected under the care of the neurology ward between September 1998 and August 2003 were retro-

spectively reviewed. Only LP samples were studied. Patients diagnosed with conditions associated with CSF hypoglycorrhachia and patients whose CSF white cell count exceeded  $20 \times 10^6$  /L were excluded. Simultaneous serum glucose was defined as the glucose concentration in blood taken within 1 hour of LP (before or after). Patients in whom a simultaneous serum glucose level was unavailable were also excluded. Blood samples were transported to the laboratory in standard fluoride/oxalate tubes. Glucose concentrations were measured by the hexokinase method on a Hitachi 747 analyser (Boehringer Mannheim, Mannheim, Germany). Fasting before LP was not mandatory. None of the patients had received concentrated intravenous glucose solution within 4 hours of LP, but infusion of glucose solution of 5% or lower was permitted as this would not affect the equilibrium between CSF and glucose levels.<sup>8</sup> Diagnosis, CSF findings (protein and glucose concentrations, white cell count), simultaneous serum glucose concentrations, and CSF to serum glucose ratios were recorded for each set of samples.

All statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 12.0; SPSS Inc, Chicago [IL], US). For group comparisons, depending on homogeneity of variance, independent-samples *t* test, one-way analysis of variance, or Kruskal-Wallis test (H-test) was applied. The relationship between CSF to serum glucose ratio and serum glucose concentration was tested with Spearman's rank order correlation coefficient.

## Results

One hundred and seventy sets of samples from 138 patients were studied (22 patients underwent more than one LP). The mean age of patients was 51.4 years (range, 19-86 years). The final diagnoses are shown in Table 1. Follow-up records for at least 1 year after LP were available in 135 patients. The remaining three patients had died—a 70-year-old man with peripheral neuropathy died of a ruptured aortic aneurysm; another patient diagnosed to have transverse myelitis died of pneumonia; the last patient had Lambert-Eaton syn-

**Table 1. Final diagnoses and related laboratory values**

Diagnosis	No. of samples, n=170	Mean values				
		CSF* glucose (mmol/L)	Serum glucose (mmol/L)	CSF to serum glucose ratio	CSF protein <sup>†</sup> (g/L)	CSF white cell count (x 10 <sup>6</sup> /L)
Peripheral or cranial neuropathies	64	4.11	7.45	0.59	0.96	2.13
Demyelination or non-infective inflammation of brain and spinal cord (eg multiple sclerosis, optic neuritis)	45	3.57	6.11	0.61	1.11	3.38
Headaches	26	3.87	6.60	0.61	0.46	1.38
Normal pressure hydrocephalus	11	4.17	6.57	0.67	0.53	1.27
Workup for neurodegenerative diseases	8	3.81	5.58	0.72	0.46	1.00
Stroke	5	4.48	10.46	0.49	0.68	5.20
Seizure	3	3.27	6.20	0.54	0.58	2.00
Others: Lambert-Eaton myasthenia syndrome (n=2), cervical myelopathy (n=1), Tolosa-Hunt syndrome (n=1)	4	3.60	5.33	0.68	0.94	2.50
Unclassified or psychosomatic disorders	4	3.65	5.13	0.71	0.65	2.29

\* CSF cerebrospinal fluid

<sup>†</sup> Significantly different (Kruskal-Wallis H-test, P<0.05)

drome and carcinoma of the lung. No brain metastasis was found on magnetic resonance imaging at the time of LP. Cytological examinations of CSF were also negative.

The overall mean CSF to serum glucose ratio was 0.61 (standard deviation, 0.142; range, 0.21-1.00), with a mean CSF glucose concentration of 3.89 mmol/L (range, 2.1-11.8 mmol/L) and simultaneous serum glucose concentration of 6.78 mmol/L (range, 3.4-27.6 mmol/L). Mean CSF protein level was 0.85 g/L (range, 0.13-4.74 g/L) and white cell count was 2.29 x 10<sup>6</sup>/L (range, 0-18 x 10<sup>6</sup>/L). The CSF glucose concentration was lower than 2.5 mmol/L in two samples: one patient with transverse myelitis had an initial CSF glucose concentration of 2.1 mmol/L but was normal on repeated LP. No infection or malignancy was identified. Another patient had associated hypoglycaemia whose CSF glucose concentration was 2.3 mmol/L and serum level was 3.4 mmol/L.

There were no significant differences among the nine disease groups in CSF to serum glucose ratio, CSF glucose concentration, serum glucose concentration, or CSF white cell count. The CSF protein level appeared higher in patients with demyelinating or inflammatory conditions (H-test, P<0.05).

Table 2 shows the number of samples with different CSF to serum glucose ratios. The ratio was lower than 0.6 in 43% and lower than 0.5 in 19% of samples. Serum glucose concentration was significantly differ-

ent among the five groups (H-test, P<0.001): the concentration was highest for samples with a ratio of lower than 0.4 and it decreased as the ratio increased. Mean CSF glucose for each group ranged from 3.55 to 4.51 mmol/L. Although the difference was statistically significant (H-test, P<0.05), a trend similar to that of serum glucose concentration was not found. The means of age (H-test, P=0.117), CSF protein level, and white cell count were not significantly different among the five groups.

Thirty sets of samples were from patients with diabetes mellitus: two controlled by diet alone, 16 on oral hypoglycaemic agents, and 12 on insulin. Their mean serum glucose concentration was 11.03 mmol/L (range, 5.8-27.6 mmol/L), compared with 5.88 mmol/L (range, 3.4-11.8 mmol/L) in non-diabetic patients (*t* test, P<0.001). The differences in CSF to serum glucose ratio and CSF glucose concentration were significant between the two groups (*t* test, P<0.05 and <0.001, respectively). The mean glucose ratio in samples with simultaneous serum glucose concentration of lower than 7.8 mmol/L was 0.65 (range, 0.44-1.00; n=132). In samples with serum glucose concentration of 7.8 to 11.1 mmol/L, the mean ratio was 0.46 (range, 0.21-0.74; n=25). In samples with serum glucose concentration of higher than 11.1 mmol/L, the mean ratio was also 0.46 (range, 0.32-0.75; n=13). The difference among the three mean ratios was significant (H-test, P<0.001). Respectively to the three groups of samples, the glucose ratio were lower than 0.6 in 31%, 84%,

**Table 2. Number and cumulative percentage of samples with different cerebrospinal fluid (CSF) to serum glucose ratios, and comparisons of serum and CSF glucose concentrations, CSF protein level, and white cell count among groups with different ratios**

CSF to serum glucose ratio	No. of samples, n=170	Cumulative percent	Mean values			
			Serum glucose* (mmol/L)	CSF glucose <sup>†</sup> (mmol/L)	CSF protein <sup>‡</sup> (g/L)	CSF white cell count <sup>§</sup> (x 10 <sup>6</sup> /L)
<0.40	11	7	11.06	3.55	0.97	1.18
0.40-0.49	22	19	10.16	4.51	0.90	2.50
0.50-0.59	40	43	6.77	3.71	0.91	2.73
0.60-0.69	52	74	5.78	3.67	0.94	2.83
≥0.70	45	100	5.27	4.10	0.64	1.44

\* Significantly different (Kruskal-Wallis H-test,  $P < 0.001$ )

<sup>†</sup> Significantly different (Kruskal-Wallis H-test,  $P < 0.05$ )

<sup>‡</sup> Not significant (One-way ANOVA,  $F = 1.086$ ;  $P = 0.365$ )

<sup>§</sup> Not significant (Kruskal-Wallis H-test,  $P = 0.187$ )

and 85%, and lower than 0.5 in 7%, 60%, and 69% (Chi squared test,  $P < 0.001$  for both ratios).

The CSF to serum glucose ratio was plotted against the simultaneous serum glucose concentration (Fig). The ratio did not remain constant but showed a strong negative correlation ( $r = -0.704$ ,  $P < 0.001$ ), which remained significant after excluding the outliers ( $r = -0.665$ ,  $P < 0.001$ ).

## Discussion

The CSF to serum glucose ratio is conventionally used to adjust CSF glucose concentration for blood glucose concentration at different glycaemic levels. Previous studies focused on patients without CSF abnormalities or with specific disorders.<sup>8,9</sup> This study included patients with a spectrum of commonly encountered neurological conditions. Many patients had a ratio below the normal range (ie  $< 0.6$  or  $< 0.5$ ). Their diagnoses and records were reviewed carefully, and none of them had any condition associated with hypoglycorrhachia. A significant negative correlation was also found between serum glucose concentration and the CSF to serum glucose ratio.

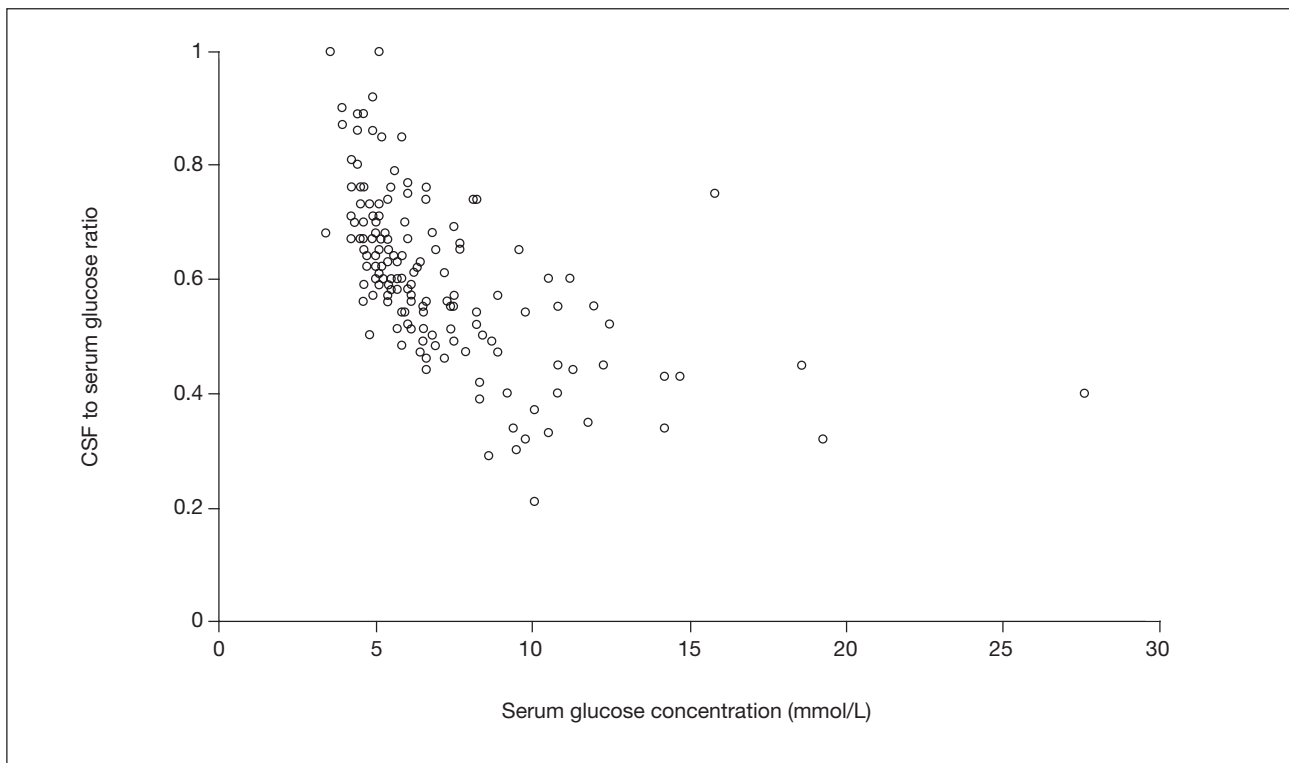
In meningitis, CSF glucose is depressed by pathogens as well as anaerobic glycolysis in adjacent neural tissue.<sup>1</sup> Glucose is also consumed by neutrophils although to a lesser extent; in order to minimise such effect in this study, case inclusion was arbitrarily cut-off at a CSF white cell count of  $20 \times 10^6$  /L. Although this did not exclude all samples with pleocytosis, patients with low glucose ratios did not have more leukocytes than those with higher ratios.

Abnormal glycolysis generates lactate.<sup>3</sup> Measurement of CSF lactate level, though not performed rou-

tinely in this study, may distinguish a false low CSF to serum glucose ratio from pathological glucose consumption. Nevertheless, elevated lactate level is not specific for meningitis; lactate also accumulates in the CSF in the presence of many other neurological and systemic diseases, including stroke, epilepsy, multiple sclerosis, cervical spondylosis, pneumonia, heart failure, uraemia, and hepatic failure.<sup>4</sup>

Concentration of glucose in CSF is mainly regulated by the choroid plexus through facilitated transportation that exhibits saturable kinetics.<sup>10-13</sup> Animal data reveal that the rate of glucose extraction increases steadily with rising blood glucose concentration.<sup>11,12</sup> In cats, when blood glucose concentration is beyond 11.1 mmol/L, the extraction rate will gradually plateau until it is saturated.<sup>12</sup> This dissociated increment was illustrated in the present study by lowering of CSF to serum glucose ratio at hyperglycaemia, although the scatterplot (Fig) failed to match a logistic regression curve expected from the saturation kinetics of glucose transportation. Conversely, a reduced glucose ratio was also present in some normoglycaemic patients. When the serum glucose level fluctuates rapidly, there is a delay of 1 to 2 hours before a steady state can be re-established in the CSF because of its slow turnover rate.<sup>8</sup> In this situation, a low glucose ratio may reflect inadequate CSF responsiveness to an upsurge in blood glucose from procedure-related stress.<sup>14</sup>

A previous group devised a linear regression normogram for ascertaining hypoglycorrhachia at various glycaemic levels (though the model could not address the deviation from linearity at high serum concentrations when glucose transportation saturates), and calculated that a CSF to serum glucose ratio of 0.6 or 0.5 could no longer be assumed when blood



**Fig. Scatterplot showing the relationship between cerebrospinal fluid (CSF) to serum glucose ratio and serum glucose concentration**

A significant negative correlation was demonstrated (Spearman's rank order correlation coefficient  $r = -0.704$ ,  $P < 0.001$ )

glucose concentration exceeded 6.9 or 10.6 mmol/L, respectively.<sup>9</sup> In the present study, glucose ratios were significantly lower, and more cases had ratios below 0.6 or 0.5 when random glucose was between 7.8 and 11.1 mmol/L or higher than 11.1 mmol/L, respectively. The latter is diagnostic of diabetes mellitus and the former indicates impaired glucose tolerance that is associated with stress-induced hyperglycaemia.<sup>15,16</sup>

One potential source of error in this study was the difficulty in controlling the time between blood sampling and determination of serum glucose concentration. Because of transportation and laboratory handling, some delay in separation of serum from red cells was inevitable. It is also well-known that glycolysis prior to separation cannot be completely inhibited by the standard fluoride/oxalate preservatives.<sup>17</sup> Simultaneous serum glucose levels in the specimens may thus have been underestimated (ie CSF to serum glucose ratio would be overestimated). Nevertheless, if the samples were tested within a few hours, a major reduction in serum glucose concentration should not be expected. More importantly, these data reflect the actual situation in clinical practice and patient management.

## Conclusion

A reduced CSF to serum glucose ratio was often seen in the absence of an appropriate neurological disorder. This is contrary to the conventional belief. The ratio may be unreliable even with modest elevations of simultaneous serum glucose level during LP. An isolated, clinically unexplained lowering of CSF to serum glucose ratio should therefore be interpreted with caution and not be overstated.

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