# Effects of Insulin and Glucose on Cytokine Production from Peripheral Blood Mononuclear Cells

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**Background:** Blood glucose levels should be controlled in patients with critical ill, regardless of whether they are diabetic. Whether hyperglycemia or insulin influences the pro-inflammatory or anti-inflammatory cytokine production in circulating cells remains unclear. In this study, we attempted to identify how hyperglycemia and insulin affect cytokine production in *in vitro*-stimulated peripheral mononuclear cells (PBMCs).

**Methods:** Nine healthy subjects were enrolled in this study. Cell cultures of stimulated PBMCs were performed with or without glucose or insulin treatment. Supernatants were analyzed for levels of interferon (IFN)-γ, interleukin (IL)-1β, IL-6, IL-10, IL-12 and transforming growth factor (TGF)-β1. The results were statistically analyzed.

**Results:** The lipopolysaccharide (LPS) stimulation significantly elevated levels of IFN-γ, IL-1β, IL-10 and IL-12 from the PBMCs. The IL-12 levels under LPS stimulation were significantly elevated after pretreatment with glucose alone, insulin alone, or a combination of glucose and insulin. However, insulin did not affect the response of IL-12 and other cytokines from hyperglycemic PBMCs.

**Conclusion:** Stimulated PBMCs with hyperglycemic status secreted more IL-12 than those with euglycemic status. Insulin treatment did not influence the IL-12 response from hyperglycemic stimulated PBMCs. More studies are needed to investigate the role of IL-12 in septic patients with hyperglycemia.
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**Key words: interleukin-12, peripheral mononuclear cells, insulin, hyperglycemia**

A large trial in a surgical intensive care unit demonstrated significant improvement in survival rates when blood glucose levels were maintained at 80-110 mg/dL.(1) Insulin therapy decreased the incidence of death in patients with sepsis, regardless of whether they had diabetes mellitus (DM). The control of blood glucose concentrations was more important than infused insulin doses.(2) Ellger et al reported that deaths in a burn-injury rabbit model were significantly lower in the two normoglycemic groups independent of insulin levels and the benefits of intensive insulin therapy mainly required mainte-

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nance of normoglycemia.[3] Acute hyperglycemia affects all major components of the immune system, such as phagocytosis and the cytokine network. In the phagocytic phase, the phagocytic function of neutrophils and macrophages is impaired in hyperglycemic patients.[4] Thus, correcting hyperglycemia may enhance bacterial phagocytosis. Another likely mechanism of improvement in survival rates is the anti-apoptotic effect of insulin. *In vivo* administration of insulin decreased post-ischemic myocardial apoptotic death.[5] The changes in cytokine responses induced by insulin or glucose may also play a role in sepsis to increase survival rates. Regardless of the type of mechanism at work, blood glucose levels should be controlled in patients with severe sepsis.[6]

Sepsis is a complicated syndrome in which pro-inflammatory and anti-inflammatory cytokines are secreted simultaneously.[7] Researchers showed increased plasma pro-inflammatory cytokine levels during hyperglycemia, whereas insulin significantly lowered pro-inflammatory cytokine levels.[8,9] Cytokine expression during sepsis includes interleukin (IL)-1β, IL-6, IL-10, IL-12 and transforming growth factor (TGF)-β1.[10] During gram-negative sepsis, interferon (IFN)-γ production was controlled at least in part by endogenous IL-12.[11] Additionally, the plasma IL-8 level correlated positively with Acute Physiology and Chronic Health Evaluation (APACHE) II score.[12] All of these cytokines are secreted from lymphocytes or monocytes/macrophages. Whether hyperglycemia or insulin alters the ability of these cytokine productions in circulating lymphocytes or monocytes/macrophages remains unknown.

Peripheral blood mononuclear cells (PBMCs) include lymphocytes and monocytes/macrophages. The aim of this study was to elucidate the effects of hyperglycemia and insulin on the cytokine productions from PBMCs using an in vitro experimental model.

## METHODS

### Subjects

From November 2005 through December 2005, nine consecutive subjects who visited the Chang Gung Memorial Hospital (CGMH), Keelung, for health examinations were enrolled. No subject had history of DM or infectious symptoms or signs. All subjects provided written informed consent.

### Isolation of PBMCs and cell culture

Whole blood (10 ml) was obtained from each subject and immediately mixed with heparin. The PBMCs were isolated from each sample via differential centrifugation over Ficoll-Plaque (Amersham Biosciences, Uppsala, Sweden) within 2 h of collection. Then, $5 \times 10^5$ PBMCs were plated in five wells of a flat-bottomed 24-well plate (Nunclon, Aarhus, Denmark) in 1 ml sterile RPMI 1640 (Gibco, Grand Island, NY, U.S.A.) tissue culture medium containing 10% heat-inactivated bovine serum and 1 mM sodium pyruvate (Gibco). The cells in the 1st well (control group) were not stimulated or treated. The cells in the 2nd well (L group) were stimulated with $1 \times 10^{-6}$ g/L lipopolysaccharide (LPS) (Sigma, Mo, U.S.A.).[13] The cells in the 3rd well (LG group) were stimulated with $1 \times 10^{-6}$ g/L LPS and treated with 4.5 g/L glucose (Sigma). The cells in the 4th well (LI group) were stimulated with $1 \times 10^{-6}$ g/L LPS and treated with 0.01 g/L insulin (Sigma).[14] The cells in the 5th well (LGI group) were treated with $1 \times 10^{-6}$ g/L LPS and treated with 4.5 g/L glucose and 0.01 g/L insulin. Plates were incubated at 37°C in 5% $CO_2$ for 68 h. Supernatants were sampled from the wells and stored at –80°C.

### Measurement of cytokines

Supernatants of IFN-γ, IL-1β, IL-6, IL-8, IL-10, and IL-12 were measured using a human enzyme-linked immunosorbent assay (ELISA) kit (Pierce Biotechnology, Ill, U.S.A.) according to the manufacturer's instructions. Supernatants of TGF-β1 were measured using a human ELISA kit (R&D Systems, Inc., Minn, U.S.A.) according to manufacturer's instructions. The intra-assay and inter-assay coefficients of variation of cytokines detection are less than 5% in our laboratory.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) V11.0.1 for Windows (SPSS, Inc., Ill, U.S.A.). Differences in cytokines levels between the groups were analyzed using Wilcoxon Signed-Ranks Test. A value of $p < 0.05$ was considered statistically significant.

## RESULTS

The mean subject age was 45 years (range, 40-68 years). Of the nine subjects, there was one woman and eight men. The levels of IFN-γ, IL-1β, IL-10 and IL-12 were significantly different among the control, L, LG, LI, and LGI groups. The LPS stimulation significantly elevated levels of IFN-γ, IL-1β, IL-10 and IL-12 (Table 1). The IL-12 levels under LPS stimulation were significantly elevated after pretreatment with glucose alone (Table 2 and Fig. 1). The IL-12 levels under LPS stimulation were significantly elevated after insulin pretreatment (Table 3 and Fig. 2).

**Table 1.** Responses of Cytokine Profiles on PBMCs under Stimulation (median and range, $10^{-6}$ g/L)

| Cytokines | No stimulation | Stimulation by LPS |
|---|---|---|
| IFN-γ | 0.00 (0.00-80.59) | 16.52 (0.00-79.40)* |
| IL-1β | 82.50 (4.47-118.98) | 442.29 (286.25-545.20)* |
| IL-6 | 596.27 (88.52-965.09) | 425.82 (314.12-792.01) |
| IL-8 | 1046.93 (862.78-1754.29) | 897.20 (808.56-1473.76) |
| IL-10 | 70.83 (15.79-404.42) | 662.84 (334.81-949.98)* |
| IL-12 | 471.01 (54.73-662.57) | 713.21 (443.49-1412.29)* |
| TGF-β1 | 1019.50 (715.92-1470.87) | 719.92 (44.85-1305.10) |

**Abbreviations:** PBMCs: peripheral blood mononuclear cells; LPS: lipopolysaccharide; IFN-γ: interferon-gamma; IL: interleukin; TGF: transforming growth factor; β: beta.
*: $p < 0.05$ compared with no stimulation by Wilcoxon Signed-Ranks Test.

**Table 2.** Effects of Glucose on Stimulated PBMCs (median and range, $10^{-6}$ g/L)

| Cytokines | Stimulation by LPS | Stimulation by LPS with glucose |
|---|---|---|
| IFN-γ | 16.52 (0.00-79.40) | 31.50 (1.65-110.22) |
| IL-1β | 442.29 (286.25-545.20) | 418.34 (218.33-520.50) |
| IL-6 | 425.82 (314.12-792.01) | 396.58 (333.09-748.01) |
| IL-8 | 897.20 (808.56-1473.76) | 945.39 (697.55-1431.59) |
| IL-10 | 662.84 (334.81-949.98) | 628.44 (274.94-1003.07) |
| IL-12 | 713.21 (443.49-1412.29) | 898.72 (733.03-1368.81)* |
| TGF-β1 | 719.92 (44.85-1305.10) | 775.84 (562.13-1161.30) |

**Abbreviations:** PBMCs: peripheral blood mononuclear cells; LPS: lipopolysaccharide; IFN-γ: interferon-gamma; IL: interleukin; TGF: transforming growth factor; β: beta.
*: $p < 0.05$ compared with no glucose treatment by Wilcoxon Signed-Ranks Test.

The levels of IFN-γ, IL-1β, IL-6, IL-8, IL-10, IL-12 and TGF-β1 from stimulated and hyperglycemic PBMCs did not change either in the presence or absence of insulin treatment. The IL-12 and TGF-β1 levels were significantly increased in LPS-stimulated PBMCs under combined insulin and glucose pretreatment, compared with those stimulated with LPS alone (Table 4 and Fig. 3). The IL-12 level from stimulated PBMCs did not differ between the presence and absence of insulin pretreatment.

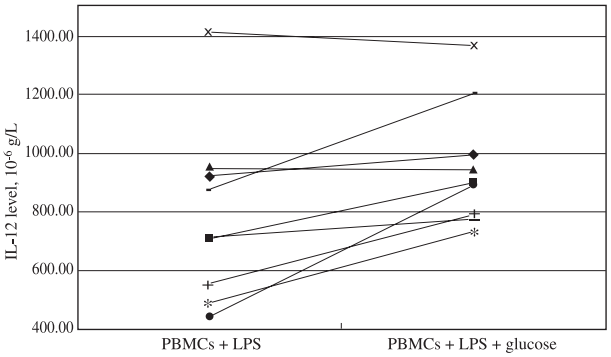


**Fig. 1** The median level of interleukin (IL)-12 in supernatant of lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs) was 713.21 x $10^{-6}$ g/L (range, 443.49-1412.29 x $10^{-6}$ g/L). The median level of IL-12 in supernatant of LPS stimulated PBMCs with glucose treatment was 898.72 x $10^{-6}$ g/L (range, 733.03-1368.81 x $10^{-6}$ g/L). The IL-12 level was significantly elevated after glucose treatment under LPS stimulation ($p < 0.05$).

**Table 3.** Effects of Insulin on Stimulated PBMCs (median and range, $10^{-6}$ g/L)

| Cytokines | Stimulation by LPS | Stimulation by LPS with insulin |
|---|---|---|
| IFN-γ | 16.52 (0.00-79.40) | 18.17 (3.30-91.26) |
| IL-1β | 442.29 (286.25-545.20) | 417.03 (288.32-656.52) |
| IL-6 | 425.82 (314.12-792.01) | 375.76 (307.00-683.73) |
| IL-8 | 897.20 (808.56-1473.76) | 902.36 (829.22-1246.58) |
| IL-10 | 662.84 (334.81-949.98) | 621.13 (271.42-994.67) |
| IL-12 | 713.21 (443.49-1412.29) | 910.28 (520.55-1656.70)* |
| TGF-β1 | 719.92 (44.85-1305.10) | 843.74 (644.02-1219.22) |

**Abbreviations:** PBMCs: peripheral blood mononuclear cells; LPS: lipopolysaccharide; IFN-γ: interferon-gamma; IL: interleukin; TGF: transforming growth factor; β: beta.
*: $p < 0.05$ compared with no insulin treatment by Wilcoxon Signed-Ranks Test.

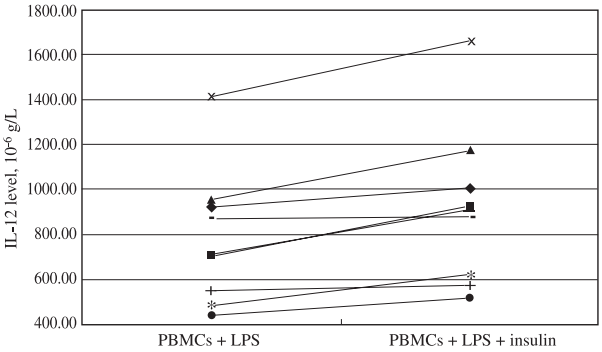


**Fig. 2** The median level of interleukin (IL)-12 in supernatant of lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs) was 713.21 x $10^{-6}$ g/L (range, 443.49-1412.29 x $10^{-6}$ g/L). The median level of IL-12 in supernatant of LPS-stimulated PBMCs with insulin treatment was 910.28 x $10^{-6}$ g/L (range, 520.55-1656.70 x $10^{-6}$ g/L). The IL-12 level was significantly elevated after insulin treatment under LPS stimulation ($p < 0.05$).

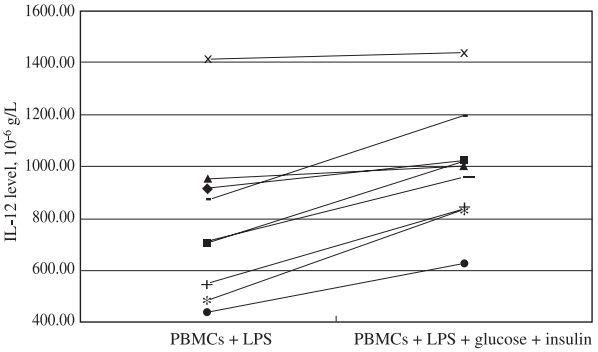


**Fig. 3** The median level of interleukin (IL)-12 in supernatant of lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMCs) was 713.21 x $10^{-6}$ g/L (range, 443.49-1412.29 x $10^{-6}$ g/L). The median level of IL-12 in supernatant of LPS stimulated PBMCs with combining glucose and insulin treatment was 1005.51 x $10^{-6}$ g/L (range, 629.54-1435.41 x $10^{-6}$ g/L). The IL-12 level was significantly elevated after combining glucose and insulin treatment under LPS stimulation ($p < 0.05$).

**Table 4.** Comparison of Cytokine Responses from Stimulated PBMCs between Those with and without Hyperglycemia and Insulin Treatment (median and range, $10^{-6}$ g/L)

| Cytokines | Stimulation by LPS | Stimulation by LPS with glucose and insulin |
|---|---|---|
| IFN-γ | 16.52 (0.00-79.40) | 18.99 (4.13-253.91) |
| IL-1β | 442.29 (286.25-545.20) | 425.83 (279.33-521.44) |
| IL-6 | 425.82 (314.12-792.01) | 352.05 (169.48-497.21) |
| IL-8 | 897.20 (808.56-1473.76) | 909.25 (815.45-1349.94) |
| IL-10 | 662.84 (334.81-949.98) | 714.04 (297.43-976.79) |
| IL-12 | 713.21 (443.49-1412.29) | 1005.51 (629.54-1435.41)* |
| TGF-β1 | 719.92 (44.85-1305.10) | 853.73 (630.04-1213.23)* |

**Abbreviations:** PBMCs: peripheral blood mononuclear cells; LPS: lipopolysaccharide; IFN-γ: interferon-gamma; IL: interleukin; TGF: transforming growth factor; β: beta.
*: $p < 0.05$ compared with no glucose or insulin treatment by Wilcoxon Signed-Ranks Test.

## DISCUSSION

The results of this study showed that levels of IFN-γ, IL-1β, IL-10, and IL-12 from PBMCs were significantly elevated after stimulation by a specific antigen, LPS. Hyperglycemia and insulin influenced IL-12 responses from LPS-stimulated PBMCs. Increased IFN-γ concentration was reported to be associated with the deaths of septic patients.[15] The IL-1β production by PBMCs on LPS stimulation was increased in survivors.[16] High IL-12 and low IL-10 production from PBMCs following in vitro stimulation were detected in survivors with sepsis.[17] The results of this work supports these findings by showing that IFN-γ, IL-1β, IL-10, and IL-12 were involved in the pathogenesis of sepsis.

The median IL-12 response was significantly elevated after glucose treatment under LPS stimulation. This result is similar to that obtained by Szelachowska et al, who showed that the peripheral blood in their patients with high-risk of insulin-dependent DM produced higher IL-12 under in vitro stimulation compared with that in the healthy control subjects.[18] In an animal model, elevated glucose promoted IL-12 cytokine gene expression in mouse macrophages.[19] Protein kinase C, p38 mitogen activated protein kinases, c-Jun terminal kinase, and nuclear factor kappa-B were involved in the pathogenesis. The plasma IL-12 p40 levels on admission in the septic patients who did not survival was significantly higher than for those who did survival.[20] Based on the results of our experiments, we proposed that high risk for death in septic patients with hyperglycemia might be associated with increased response of IL-12 from peripheral blood.

This is the first study in which the results showed that insulin enhanced the IL-12 response from LPS-stimulated PBMCs. The mechanism accounting for this response, however, remains unclear. In this work, the IL-12 response from hyperglycemic LPS-stimulated PBMCs did not differ between those treated with and without insulin. The response of IL-12 from LPS-stimulated PBMCs increased after pretreatment with glucose, insulin, or combined glucose and insulin. The findings indicated that insulin did not affect the response of IL-12 from hyperglycemic PBMCs. No previous investigation supports our findings. Consequently, additional studies are needed to confirm this hypothesis.

The findings regarding the role of TGF-β1 levels in predicting the survival rate of patients with severe sepsis are contradictory. Lekkou et al reported that the TGF-β1 levels were significantly elevated in non-survivors with severe sepsis.[21] However, Monneret et al showed that the TGF-β1 levels had no prognostic power for patients with septic shock.[22] The prosclerotic cytokine TGF-β1 has been implicated as an important downstream mediator in the progression of pathological renal changes occurring in diabetic patients. The study by Viswanathan et al demonstrated that, compared with non-DM subjects, serum TGF-β1 levels were significantly elevated in patients with type 2 DM.[23] In the same study, DM patients treated with insulin had significantly lower TGF-β1 levels compared with those in patients not treated with insulin. In our study, the TGF-β1 response did not change in stimulated PBMCs after treatment with glucose or insulin. However, the TGF-β1 levels significantly increased in LPS-stimulated PBMCs under combined insulin and glucose pretreatment, compared with those stimulated with LPS alone. Insulin in this study enhanced TGF-β1 production in hyperglycemic stimulated PBMCs. This finding is opposed to that reported by Viswanathan et al. A possible explanation is that TGF-β1 was secreted not only from the mononuclear cells but also from most other cells. The other explanation is the difference in the data between *in vivo* and *in vitro*. Another explanation is that the culture medium used for this experiment contained fetal calf serum. This is a source of the background level of TGF-β1. Although a control group was included for the analysis, fetal calf serum as a part of culture medium might influence TGF-β1 response from PBMCs.

Increased release of IL-6 from monocytes in a setting of hyperglycemia has been reported, and the possible mechanism was via induction of protein kinase c-α and β.[24] When monocytes from patients with type 1 DM were stimulated with LPS, an increased tendency to produce acute phase cytokine IL-6 was observed compared that of healthy control subjects.[25] Large scale investigations may be needed to determine the effects of glucose on IL-6 response from PBMCs. Monocytes/macrophages secret IL-12 and IL-12 induces type 1 T helper (Th1) lymphocyte formation. The IL-12 production from PBMCs was increased in hyperglycemic status in our study. The higher IL-12 level may enhance Th1 cell gene expression, such as IFN-γ production. However, IFN-γ production from PBMCs was not influenced by hyperglycemic status. The possible cause might be that the sources of IFN-γ were CD8+ T lymphocytes, Th1 lymphocytes and natural killer cells. The synthesis of IFN-γ was not completely controlled by IL-12.

In conclusion, the results of this work demonstrated that IL-12 responses from PBMCs were influenced by glucose and insulin. Insulin did not decrease the hyperglycemic effects on IL-12 responses from LPS-stimulated PBMCs. Further investigations are needed to elucidate the effects of different concentrations of glucose and insulin on cytokine production from PBMCs using time-course *in vitro* experiments and flow cytometry analysis of the cell types.

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# 胰島素和葡萄糖對體外刺激周邊血液單核淋巴球產生細胞激素的影響

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**背 景：** 對於嚴重敗血症的病患，無論他們是否是患有糖尿病，血糖應該被控制。高血糖或胰島素是否影響循環細胞產生發炎激素與抗發炎激素仍不清楚。這個研究嘗試確認胰島素和葡萄糖對體外刺激周邊血液單核淋巴球產生細胞激素的影響。

**方 法：** 九名健康人參與此研究。將刺激周邊血液單核淋巴球加以培養，並分別投予葡萄糖或胰島素。培養皿的上清液拿來分析丙種干擾素、細胞間介素 -1$\beta$、細胞間介素 -6、細胞間介素 -10、細胞間介素 -12 與生長轉換因子 -$\beta$1 的濃度，並將結果加以統計分析。

**結 果：** 細胞間介素 -12 濃度在給予葡萄糖後明顯上升，細胞間介素 -12 濃度在給予胰島素治療後也明顯上升。在高血糖的情況下，即使加入胰島素，細胞間介素 -12 濃度並無變化。同時給予葡萄糖與胰島素，細胞間介素 -12 濃度會上升。血糖或胰島素對周邊血液單核淋巴球產生丙種干擾素、細胞間介素 -1$\beta$、細胞間介素 -6、細胞間介素 -10 與生長轉換因子 -$\beta$1 的量是相近的。

**結 論：** 與正常血糖狀態比起來，周邊血液單核淋巴球在高血糖情形下產生較高的細胞間介素 -12。對於在高血糖情形下的周邊血液單核淋巴球，胰島素的治療並不影響細胞間介素 -12 的產生。需要更多的研究來探索細胞間介素 -12 在高血糖敗血症病患的角色。

(長庚醫誌 2008;31:253-9)

**關鍵詞：**細胞間介素-12，周邊血液單核淋巴球，胰島素，高血糖

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