

*Review Articles*

## **Role of Inflammatory Marker Interleukin 6 (IL-6) and Insulin in Diabetes and Diabetic Neuropathy**

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### **Abstract**

**Introduction :** Circulating IL-6 levels have been reported to be elevated in subjects with type 2 diabetes. Diabetic peripheral neuropathy is a common complication of diabetes in 66% of type I and 59% of type 2 diabetics.<sup>1</sup> Diabetic polyneuropathy is the most commonly acquired diffuse disorder of the peripheral nervous system.<sup>2</sup>

**Aim :** This study is focussed on the correlation between serum Interleukin-6 (IL-6), serum insulin and glycaemic status.

**Methods and Patients :** Twenty-three subjects were selected for the study. Out of the total subjects, 17 were with type 2 diabetes mellitus and 6 with diabetic neuropathy. Two subjects with diabetic neuropathy had given consent for neurolysis. Blood sugar level was estimated by standard method. Serum IL-6 and insulin levels were measured by ELISA method. Attempts were made to elucidate the relationship between glycaemic status (or insulinaemia) and with diabetic neuropathy and neurolysis.

**Results :** Results show that there is no direct relationship between fasting blood sugar and IL-6 however, raised IL-6 was observed in 66.66% diabetic and in 50% with diabetic neuropathy. It was observed that though patients with diabetes were within glycaemic control raised IL-6 levels revealed the presence of inflammation. Such patients should be followed up for early detection of neuropathy.

**Conclusion :** Raised IL-6 levels in diabetics with glycaemic control revealed the presence of inflammation. Such patients should be followed up further to prevent neural damage.

### **Introduction**

The pathogenesis of type 2 diabetes is characterized by a combination of insulin resistance at the level of skeletal muscle, fat, and liver, and failure of pancreatic  $\beta$ -cells to compensate for the enhanced insulin demand. A body of evidence has accumulated over the past decade supporting the concept that insulin resistance and type 2 diabetes are related to a chronic, low-grade, inflammatory

state. Circulating IL-6 levels have been reported to be elevated in subjects with type 2 diabetes<sup>1</sup> and correlate with direct and indirect measures of insulin resistance.<sup>2,3</sup>

Diabetic peripheral neuropathy is a common complication of diabetes in 66% of type I and 59% of type 2 diabetics.<sup>4</sup> Diabetic polyneuropathy is the most commonly acquired diffuse disorder of the peripheral nervous system. It is generally assumed that insulin benefits human and experimental diabetic neuropathy indirectly by lowering glucose levels. Insulin also provides potent direct support of neurons and axons, and

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there is a possibility that abnormalities in direct insulin signaling on peripheral neurons relate to the development of this disorder.<sup>5</sup>

Chronic inflammation has been postulated to play a role in the pathogenesis of type 2 diabetes.<sup>6</sup> Sharma *et al*<sup>7</sup> explored the antinociceptive effect of insulin and its combinations with resveratrol and curcumin in attenuating diabetic neuropathic pain. The study also examined the effect of these combinations on tumour necrosis factor-alpha (TNF-alpha) and nitric oxide (NO) levels in streptozotocin (STZ) induced diabetic mice.

Outcome of decompression of peripheral nerves in diabetics has been documented<sup>8-10</sup> in literature, however, reports regarding correlation between diabetes, diabetic neuropathy, serum insulin and IL-6 are scarce.<sup>11</sup>

### **Aim**

This study is focussed on the correlation between serum Interleukin-6 (IL-6), serum insulin and glycaemic status.

### **Methods and Patients**

Twenty-three subjects were selected for the study. Out of the total subjects, 17 were with type 2 diabetes mellitus and 6 with diabetic neuropathy. Two subjects with diabetic neuropathy had given consent for neurolysis. Blood sugar level was estimated by standard method. Serum IL-6 and insulin levels were measured by ELISA method. Attempts were made to elucidate the relationship between glycaemic status (or insulinaemia) with diabetic neuropathy and neurolysis. The initial management consisted of measures aimed at controlling the diabetic status. Thorough assessment of the peripheral neuropathy was done by an independent neurologist and by recording the electromyogram (EMG) and nerve conduction studies.

Patients having diabetic foot problems secondary to Diabetic Peripheral Neuropathy with an intact circulation were included. Those having ischaemic or neuro-ischaemic foot problems secondary to occlusive peripheral vascular disease were excluded.

Excluding those cases having macrovascular obstructive pathology, all cases, of "diabetic distal symmetric polyneuropathy" were offered decompression of the posterior tibial nerve, artery and veins and lateral popliteal nerve as a safeguard against future foot problems. This was undertaken after the control of infection or after complete healing of the presenting foot lesion.

### **Results**

Results show that there is no direct relationship between fasting blood sugar and IL-6 however, raised IL-6 was observed in 66.66% diabetic and in 50% with diabetic neuropathy. No correlation was found between the blood sugar level, IL-6 and serum insulin levels (Figs. 1 and 2). IL-6 concentration was estimated before and after neurolysis showed significant reduction in IL-6 suggesting that the inflammation has been resolved by neurolysis and the prognosis is better in these patients. In other cases no direct correlation was observed because of the better diabetic control.

It was observed that though patients with diabetes were within glycaemic control raised IL-6 levels revealed the presence of inflammation. Such patients should be followed up for early detection of neuropathy.

A multiple regression analysis showed no correlation with hyperglycaemia. However, serum IL-6 levels lowered after the surgery in two cases. Serum IL-6 and insulin levels differed in diabetic and diabetic neuropathy group however, the difference was not significant.

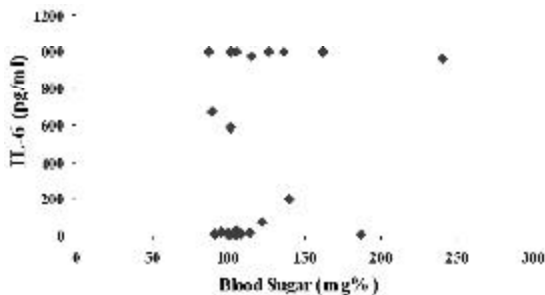


Fig. 1 : Correlation between blood sugar and IL-6

### Case 1

A 64 years male with history of shoe bite (Rt) foot developed diabetic gangrene of 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> toe with extensive necrotizing fasciitis (Rt) foot dorsum. He had diabetic nephropathy also. He had oesophageal varices and was on dialysis.

He had H/o D.M. and IHD for 15 years and had undergone CABG 2 years ago.

Surgery : Debridement and skin grafting followed by neurolysis

On examination : Pulse 78/min and Blood pressure 130/80 mm Hg RR 18/min.

On investigating, Haemoglobin was 11.5 gm%. Other parameters : Blood sugar 114 mg%, cholesterol 77 mg%, Alkaline phosphatase 140 mg%, Creatinine 7.9 mg%, Uric Acid 12.2 mg%, Total proteins 6.5 gm%, Urea 254 mg%. Serum Mg 2.9 mg%. Na 128, K 5.5 and Cl 91. Urine examination showed 20-30 pus cells and pus showed rich growth of psuedomonas. Serum acetone 50 mg%.

He was on the following medication: Ecosprin 150 mg OD, Clopitab 75 mg BD, TTGTOR 1 OD, PAN 1 BD, Ramistove 1 OD. HAI 6-6-4.

IL-6 levels before surgery : 29.8 pg/ml and after surgery :12.7 pg/ml

Serum insulin levels before surgery : 243.7 mIU/ml and after surgery : 91.03 mIU/ml

### Case 2

A 56 years male with history of plantar ulcer (Lt foot) 8 years ago debridement was done of the 6 cm diameter ulcer in the region of metatarsal heads in the forefoot.

He had H/o D.M. and IHD for 12-15 years.

Surgery : During hospitalization, he had undergone debridement of the ulcer and amputation of Lt 2<sup>nd</sup> toe which was totally engulfed in a verrucose

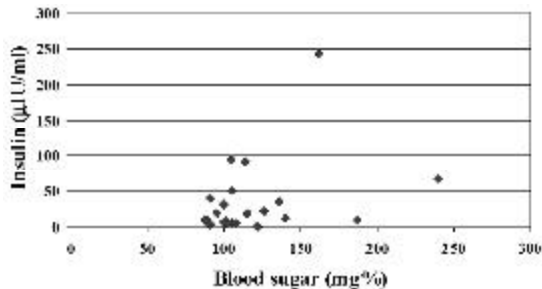


Fig. 2 : Correlation between blood sugar and insulin

lesion and neurolysis of the lateral popliteal nerve.

On examination : Pulse 76/min and Blood pressure 140/80 mm Hg RR 18/min.

On investigating, Haemoglobin of 13.0 gm%. Other parameters : Blood sugar 91 mg%, ESR 54mm at 1 hr, Cholesterol 151 mg%, Alkaline phosphatase 104 mg%, Creatinine 1.0 mg%, Urea 15 mg%. Na 139, K 4.8 and Cl 104.

2D Echo showed sclerotic valve with LVEF 60%. ECG showed ST elevation. Hb A1C 8.3% .

He was on the following medication: Tramazac, Ceftop, Diapride forte 1 OD, Stiloz Melcovit Hosit Nugrel HAI 32 - 0 - 30.

IL-6 levels before surgery : 6.7 pg/ml and after surgery : 0.3 pg/ml

Serum insulin levels before surgery : 6.36 mIU/ml and after surgery : 3.40 mIU/ml

### Discussion

Results show that in type 2 diabetic subjects there was no direct relationship between fasting/ post prandial blood sugar and IL-6 however, raised IL-6 was observed in most of the diabetic as well as diabetic neuropathy patients.

Shiraiwa<sup>12</sup> observed that post-prandial hyperglycaemia, rather than fasting glycaemia or haemoglobin A1c levels, is an important predictor of the incidence of diabetic microangiopathy in Japanese type 2 diabetic patients .

Though sugar levels were normal, the inflammation the root of all evils in diabetes and the Dysmetabolic Syndrome Insulin resistance were associated with elevations of

inflammatory mediators such as interleukin-6.<sup>13</sup>

Raised IL-6 was observed in 66.66% diabetic and in 50% with diabetic neuropathy however, none of the subjects showed insulin resistance.

Shiraiwa *et al*<sup>12</sup> reported that though diabetic microangiopathy is often observed in diabetic patients, there is little evidence regarding the relationship between post-prandial glycaemia or insulinaemia and the incidence of diabetic microangiopathy.

Another study from Italy<sup>14</sup> reported evidence about diabetic microangiopathy which enabled identify an integrated pathogenesis of diabetic complications, including classic metabolic pathways induced by hyperglycaemia, insulin-resistance, hyperinsulinaemia, hormonal alterations and growth factors. Oxidative stress is the most important cause of endothelial damage inducing leucocyte adhesion, altered coagulation and inflammation.

The progressive nature of type 2 diabetes is not related to further increase in insulin resistance but rather to a decline in beta-cell function. The mechanism of beta-cell dysfunction appears to include inflammation involving TNF $\alpha$ , C-reactive protein, increased white blood cell count and erythrocyte sedimentation rate, autoimmunity (GAD antibodies) in the LADA syndrome, and a replacement of islets by islet amyloid protein.

All therapies thus far have addressed the insulin-resistant component of type 2 diabetes or have been directed at stimulating beta cells or changing hepatic glucose output.

It has been reported<sup>15</sup> that improvement in health status and mood may be associated with basal/bolus, but not twice-daily, insulin in elderly type 2 subjects. These effects may

be independent of glycaemic control.

Study by Nakano<sup>16</sup> suggested that marked autonomic dysfunction, rather than other confounding factors, is related to increased insulin resistance in DM.

In our study IL-6 levels were raised in 66.66% in type 2 diabetics and 50% with neuropathy.

However, González-Clemente<sup>17</sup> showed that in type 1 diabetes, cardiovascular autonomic neuropathy (CAN) is associated with cardiovascular risk factors related to insulin resistance, which in turn are associated with low-grade systemic inflammation. Reduced heart rate variability (HRV) is considered one of the first indicators of CAN.

A significant negative correlation was found between E/I ratio and plasma concentrations of IL-6 suggesting a link between low-grade inflammation and early alterations of CAN in type 1 diabetes and may be of importance in the pathogenesis of CAN and/or its clinical implications.

Outcome of decompression of peripheral nerves in diabetic has been documented in literature, however, reports regarding correlation between diabetes, diabetic neuropathy, serum insulin has not been reported. There are studies referring to various aspects viz: Huang *et al*<sup>18</sup> have proposed mitochondrial dysfunction as a mediator of neurodegeneration in diabetes complications. The results demonstrate that loss of insulin-dependent neurotrophic support may contribute to mitochondrial membrane depolarization in sensory neurons in diabetic neuropathy.

Serum IL-6 and insulin levels differed in diabetic and diabetic neuropathy group however, the difference was not significant. It may be due to less number of patients in

diabetic neuropathy group and none of our patients were obese. Mavridis *et al*<sup>19</sup> reported low-grade chronic inflammation, as estimated by the relative levels of inflammatory cytokines, in patients with type 2 diabetes that were receiving insulin treatment, with significantly higher cytokine levels recorded compared to sulphonylurea-treated patients. In addition, an association between inflammation and both obesity and glucose homeostasis was detected.

However, while the relationship between insulin resistance and circulating IL-6 levels is well established, there is little information on an independent association between plasma IL-6 levels and insulin secretion.<sup>3</sup> Conflicting results have also been reported from in vitro studies, showing that IL-6 has stimulatory,<sup>20-22</sup> neutral,<sup>23</sup> or inhibitory<sup>24,25</sup> effects on insulin secretion from pancreatic  $\beta$ -cells, likely as a result of a wide variability in experimental conditions. The relationship between IL-6 and insulin secretion appears to be independent of modulators of insulin secretion such as age, sex, BMI, and insulin sensitivity. The relationship between IL-6 and insulin action seems to be partially mediated through adiposity.

There was significant reduction in IL-6 after surgery in two subjects, indicating that the inflammation has been resolved by neurolysis and the prognosis is better in these patients. In other cases no direct correlation was observed because of the better diabetic control. A multiple regression analysis showed no correlation hyperglycaemia. However, serum IL-6 levels lowered after the surgery in few cases.

It was observed that though patients with diabetes were within glycaemic control with raised IL-6 levels revealed the presence of inflammation. Such patients should be followed up for early detection of neuropathy.

## Conclusion

Raised IL-6 levels in diabetics with glycaemic control revealed the presence of inflammation. Such patients should be followed up further to prevent neural damage. Improvement of IL-6 levels after neurolysis indicated controlled inflammation and better prognosis in such patients.

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