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# NON DIABETIC USES OF INSULIN

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## ABSTRACT

Insulin is the most important anabolic hormone in the body made by the pancreas that allows your body to use sugar (glucose) from carbohydrates in the food that you eat for energy or to store glucose for future use. Insulin helps keeps your blood sugar level from getting too high (hyperglycemia) or too low (hypoglycemia). This brief communication reviews the non-diabetic uses and utility of insulin.

**KEYWORDS:** Insulin, Nonendocrinal uses, applied pharmacology.

## INTRODUCTION

Insulin is the most important anabolic hormone in the body made by the pancreas that allows your body to use sugar (glucose) from carbohydrates in the food that you eat for energy or to store glucose for future use. Insulin helps keeps your blood sugar level from getting too high (hyperglycemia) or too low (hypoglycemia). The discovery of insulin by Banting and Best, almost a century ago, changed the scenario in the treatment of Diabetes Mellitus (DM). Over the past century, researchers have discovered multiple pleiotropic effects and actions of this molecule. But besides DM, multiple non-diabetic uses of this hormone also have been discovered and suggested. Some of these reviewed non-diabetic uses of insulin are as follows.

### Cardiology

Glucose–insulin–potassium solution (GIP or GIK solution) is given after a myocardial infarction to increase the usage of glucose by the myocardium and maintain the integrity of membrane ionic pumps.[1] The GIP solution provides the glucose needed by the myocardium in reperfusion conditions and protects the cellular membrane and keeps the membrane pumps functional. Insulin facilitates potassium reuptake into the myocardial cells and thus stabilizes them, which results in a lower occurrence of arrhythmias after Myocardial Infarction (MI).

Positive inotropy is partially dependent on increased glucose uptake. Normally free fatty acids are main substitutes metabolised by myocardial cell, but when given as Glucose Insulin-Potassium infusion (GIK), glucose becomes the main substrate for energy in mycordium due to decreased availability of circulating free fatty acids & enhanced myocardial glucose uptake. This decreases the oxygen requirement.[2,3,4,5] Systemic insulin administration results in a reduction of circulating free fatty acids and an improvement in myocardial glucose uptake, which causes an efficiency improvement in the myocardial cell.

To prevent the drop in blood glucose levels, insulin administration is combined with infusion of glucose; and potassium is usually added to prevent hypokalaemia caused by simultaneous entry of potassium into the cell with glucose. During GIK administration, the uptake of free fatty acids was reduced thereby decreasing the oxygen requirement which is beneficial in ischemic heart disease. Insulin keeps blood vessels to brain healthy and allows the brain to function normally. Deficiency of insulin or insulin resistance impairs the cognitive functions (especially verbal ) of brain & has been implicated in the formation of plaques in Alzheimer's Disease (AD). So AD is also known as Type 3 DM.[6] Studies have shown that exogenous insulin administration improves memory both in healthy volunteers and those suffering from AD. Lack of insulin signaling in the brain may lead to changes in Akt and GSK3 activity and Tau hyperphosphorylation but must interact with other mechanisms for development of Alzheimer's disease. There is a common cellular pathway in the neurodegenerative diseases with abnormal mitochondrial function and abnormal glucose metabolism. This common pathway involves

Peroxisome Proliferator Activated Receptor (PPAR)-gamma, a key regulatory enzyme involved in mitochondrial resistance and insulin resistance. So insulin supplementation can be useful in Parkinson's disease and Huntington's disease.[7,8]

High glutamate levels are associated with increased risk of stroke. This has been reiterated by the fact that glutamate scavenger oxaloacetate decreases the risk of acute ischaemic stroke.[9] Insulin causes reduction in circulatory amino acids including glutamate & thereby proves useful in acute ischaemic stroke treatment. Previously insulin was also used in narco analysis to reduce an individual's self-control over one's thought and cause him to reveal the true thoughts & feelings which the person would have suppressed. Its use in Schizophrenia has been obsoleted due to availability of better drugs.[10,11] Experimental data establish the effectiveness of insulin treatment in improving neurologic recovery in spinal cord injury , increasing the expression of anti -apoptotic bcl-2 proteins, inhibiting caspase-3 expression decreasing neuronal apoptosis, reducing the expression of proinflammatory cytokines iNOS and COX-2, and ameliorating microcirculation of injured spinal cord after moderate contusive spinal cord injury in rats. The studies report the beneficial effects of insulin in the treatment of spinal cord injury , with the suggestion that insulin should be considered as a potential therapeutic agent. The central nervous system has an absolute requirement for glucose. A reduction in blood glucose level causes a decrease in all the higher mental functions. Narco analysis uses this principle to reduce the higher mental control on the thoughts or memories.

**Anti-aging effect**

Klotho (KL), an antiaging protein, was named after the goddess who spins the threads of life. Mice lacking KL exhibit many changes that occur during aging include atherosclerosis, osteoporosis, infertility, and cognitive decline. They also have a shorter life span. In contrast, mice over expressing KL live 30% longer than wild-type mice and are more resistant to oxidative stress.[12] Insulin has also been associated with an increased release of Klotho, the anti-aging protein.[13] It is an area which needs further research before it can be used practically.

**Growth and anabolic action**

Hormones such as insulin, insulin-like growth factors, thyroxine and the glucocorticoids act as nutritional & maturational signals and adapt fetal development to prevailing intrauterine conditions, thereby maximizing the chances of survival both in utero and at birth.[14,15] Insulin is required for the growth even in foetal stage. Its deficiency leads to low birth weight, decreased crown -rump length at birth, fetal growth retardation in uterus.[14] Insulin has been used in the provocative test for the diagnosis of Growth Hormone (GH) deficiency. When insulin is given, blood glucose levels decrease & in normal conditions GH is released because GH is counter regulatory hormone. Failure to rise of GH in response to insulin suggests GH deficiency.

**Nutrition**

The solutions used for total parenteral nutrition often contain a small amount of insulin.[16] Regular insulin added to parenteral nutrition solution manages hyperglycemia, improves absorption of nutrients and reverses negative protein balance. Insulin availability in such solutions ranges from 10 to 95%. Rapid infusion of the parenteral nutrition, as is the usual case, would cause severe hypoglycemia if the insulin were not there to cause the glucose to be absorbed rapidly into the cells. It also prevents other complications such as muscle wasting which are common in bed-ridden patient.

**Potentiation of Chemotherapeutic Agents.**

The effect of insulin and Insulin like Growth Factor (IGF-1) on cellular responses to chemotherapeutic drugs (5-fluorouracil, oxaliplatin and irinotecan) in colon cancer and endothelial cells was analysed in vitro and they were shown to modulate the cellular responses.[17,18] It might be due rapid cell division phase in which these agents act.[19] Use of low doses of chemotherapeutic agents with increased frequency along with insulin suggest another method called Insulin Potentiated Therapy (IPT) or now called Insulin Potentiated Targeted Low-Dose therapy (IPTLD). In IPTLD 10 times lower doses of chemotherapeutic agents are given at shorter intervals. This treatment has very low toxicity and efficacy was same as that of standard chemotherapy. So it improves the quality of life.[21]

**Malignancy**

Insulin potentiation therapy (IPT) is a controversial, innovative cancer treatment which combines insulin with low-dose chemotherapy to prevent toxic effects and chemoresistance.[5] With IPT, dose-related adverse effects of chemotherapeutic drugs are prevented and anti-neoplastic effects are increased specifically. However, its effectiveness is still debatable and this has limited its wide usage.

**Anti-inflammatory**

Diabetes is characterized by a pro inflammatory state, and several inflammatory processes have been associated with both type 1 and type 2 diabetes and the resulting complications. The research data illustrate the anti-inflammatory effects of insulin and proinflammatory effects of glucose.[4] & provide mechanistic justification for the benefits of maintaining euglycemia with insulin infusion in patients with inflammation.[13] Insulin has anti-inflammatory action predominantly by reducing the IL-6, IL-18 & TNF – alpha production via Mitogen Activated Protein Kinase (MAPK) pathway & mTOR pathway respectively. Insulin decreases the leucocyte adherence

to endothelium via AKT pathway; (as shown in Figure 1) and also enhances phagocytosis thereby arresting the bacterial growth. Hence Protamine Zinc Insulin (PZI) is used to facilitate the wound healing in open wounds, surgical incision and laceration.[22,23]

Studies have proved that if insulin is added to human cell culture, it stimulates the proliferation and migration of keratinocytes and in micro vascular culture it promotes migration of cells.[20]

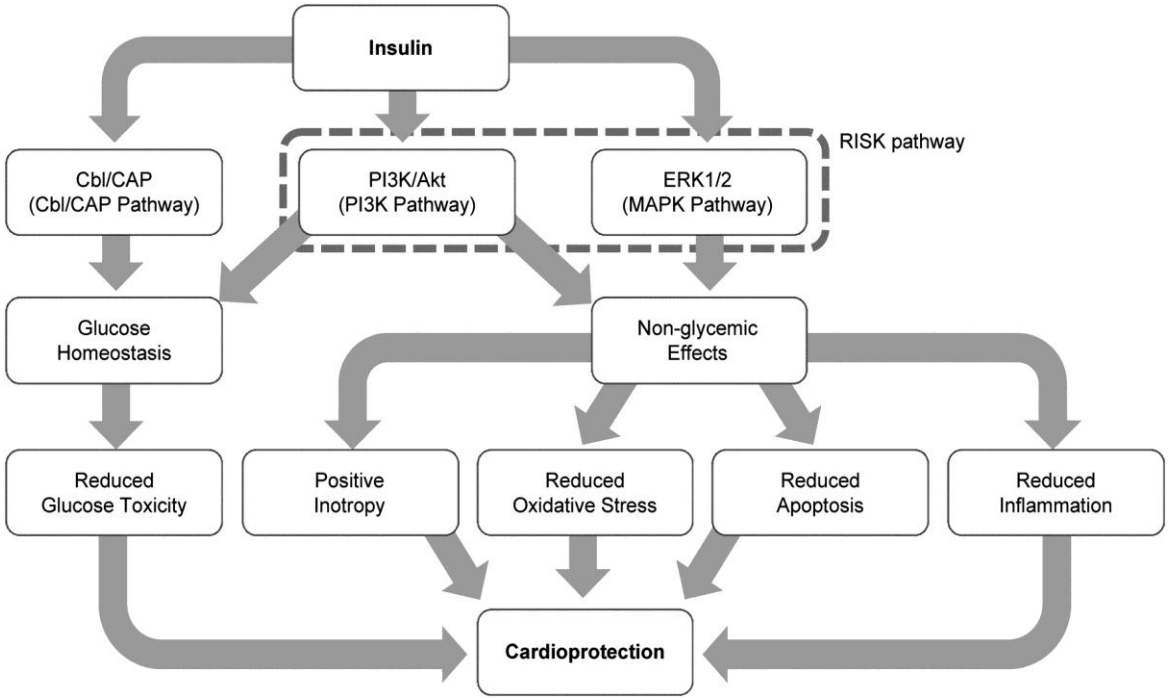


**Figure 1: Insulin: modes of non-endocrinal actions.**

{CAP indicates Cbl-associated protein; PI3K-phosphatidylinositol3-kinase; ERK1/2-extracellular signal-regulated Kinase; RISK- reperfusion injury salvage kinase; and MAPK- mitogen-activate protein kinase.}

## CONCLUSION

The conventional role of insulin in carbohydrate metabolism is well known since decades. Surely enough, the discovery of insulin did change the course of treatment of diabetes altogether and even today its major use comes in diabetes, but the diversity of applications of insulin suggests that it has the potential of curing many more diseases than previously anticipated.

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