Observational Study

Nondiabetic uses of insulin

Amit Nachankar[1], KVS Hari Kumar[1]

Insulin is the key hormone in the fuel metabolism of the body. Insulin is the cornerstone in the management of patients with diabetes during the last century. The use of insulin beyond diabetes has been described in many situations. Insulin has been used in many situations as a diagnostic and therapeutic agent beyond the diabetes. In this article, we present the non-diabetic uses of insulin that have been described in the clinical practice.

[*J Indian Med Assoc* 2018; **116:** 47-9]

Key words **: Insulin; Diabetes; Schizophrenia; Hypopituitarism; Hyperkalemia.**

Insulin is a potent anabolic hormone secreted by beta cells of pancreas and is most commonly used as antidiabetic therapy. It was discovered in 1921by Banting & Best & they received Nobel prize for the same in 1923. Its molecular structure was determined by Sanger in 1951. Apart from the antidiabetic use, insulin is also used in a variety of situations as a diagnostic and therapeutic agent as shown in Table 1[1]. The exact mechanism for its action for nondiabetic used is as follows[2] :

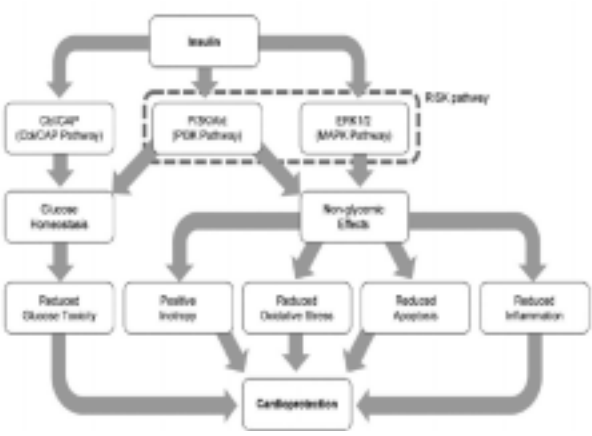
Diagnostic uses	**Therapeutic uses**
Diagnosis of Growth Hormone Deficiency	Hyperkalemia management
Diagnosis of ACTH Deficiency	Myocardial reperfusion
Growth Medium for cell cultures	Nutrition
Narcoanalysis	Wound Healing
	Anabolic abuse
	Antidote
	Insulin Potentiation therapy
	Schizophrenia
	Septic shock
	Aging

Diagnostic Uses of Insulin :

Pituitary hormone deficiency syndromes: Insulin tolerance test (ITT) is a gold standard for growth hormone assessment[3]. Being at risk of seizures and death, it is uncommonly performed in clinical setting. The advantage being simultaneous assessment of cortisol axis to rule out secondary adrenal insufficiency[4,5]. It is contraindicated in the elderly, in patients with cardiovascular or cerebrovascular diseases, history of seizures, an abnormal electroencephalogram, recent brain surgery, and severe hypopituitarism[6,7]. ITT is also used to differentiate Cushing's syndrome from Pseudo Cushing states[6].

Cell cultures: Insulin is also used as a growth medium for a variety of cell cultures. It increases glucose transport across cell membrane, thereby improving cell survival.

[1]Department of Endocrinology, Army Hospital (R&R), Delhi Cantt, New Delhi 110010



Insulin is also an important component of organ preservation solutions used for transplants. Additionally, insulin is used for narcoanalysis by causing hypoglycemia thereby decreasing higher mental functions. Insulin is required for the growth and development of cells[8] and also stimulates the proliferation of certain cells in culture[9]. Insulin is used as an essential component of synthetic growth media for cell culture[10]. Insulin has been found to be stimulatory in serum-free medium for the growth of virtually every cell type including mammalian cells[11]. It is used for the manufacture of monoclonal antibodies, virus vaccines, gene therapy products, and other biological drugs[12].

Therapeutic Uses of Insulin :

Hyperkalemia : Glucose insulin infusion is commonly used to correct hyperkalemia.

Glucose insulin potassium infusion is also used in post myocardial infarction, to improve the myocardial reperfusion thereby prolonging the myocardial viability.

Myocardial infarction : Glucose insulin potassium (GIK) infusion helps in myocardial reperfusion post myocardial infarction by ensuring glucose delivery to myocardium and maintaining ionic pump integrity[13]. GIK infu-

sion was one of the first agents to be studied for protection of the ischemic myocardium that will reduce myocardial infarct size and improve clinical outcomes[14]. The immediate myocardial metabolic enhancement during initial assessment and treatment in emergency care (IMMEDIATE trial) assessed the impact of GIK on acute coronary syndromes in prehospital emergency medical service settings in the ambulance by the paramedics and showed that progression to infarction (by biomarkers and ECGs), the primary endpoint, was not prevented, but infarct size was significantly diminished, and there was significant reduction of free fatty acid levels and acute mortality rate.

Nutrition: Insulin is a component of total parenteral nutrition which helps to absorb nutrients into cells thereby preventing severe hyperglycemia[15]. Insulin plays a key role in protein anabolism as it enhances the rate of amino acid uptake and protein synthesis in muscles and also inhibits the extent of protein degradation[16,17]. Deficiency of insulin results in muscle wasting and increased nitrogen balance in bed-ridden patients. A study showed that addition of insulin to PN solutions accelerated restoration of a depleted body cell mass[17].

Wound Healing: Topical application of insulin has shown to enhance wound healing in both diabetic and non-diabetic subjects[18]. Sensory organs, central and peripheral nervous system, vestibule and palate of mouth, tongue, nose, nails, hairs, sweat and sebaceous glands, eyes and the ears are specially benefitted. Zinc protamine insulin (ZPI) accelerates wound healing in open wounds, surgical incisions and lacerations[19]. Insulin helps in cellular proliferation in devitalized tissues. After removal of the exudate and necrotic tissue, insulin enhances the metabolism of adjacent layer and stimulates regeneration and proliferation. It also arrests bacterial growth and accelerates phagocytosis, thereby lowering the risks of infection.

Anabolic use: often insulin is abused by many sportspersons to increase the muscle bulk often in combination with growth hormone and anabolic steroids[20]. Glycogen is the primary source of carbohydrate during exercise. Sport performance is a function of muscle glycogen stores; 'bulking up' these stores will most probably enhance performance, ie, the greater the muscle glycogen stores, the longer the exercise time to exhaustion[21]. Insulin increases protein synthesis in the muscle by increase in amino acid transport and ribosomal protein synthesis. It also increases glycogen synthesis by increasing transport of glucose and inducing glycogen synthase enzyme[22]. Physiological hyperinsulinemia reportedly stimulates amino acid transport in human skeletal muscles[23]. It is very difficult to detect insulin abuse using laboratory tests because of its short half-life[24].

Antidote : In calcium channel blocker and beta blocker poisoning (Amlodipine atenolol combination or verapamil overdose), insulin dextrose infusion has been shown to stabilize the hemodynamic changes, thus enhancing recovery[25]. Insulin has positive inotropic effect by glucose delivery to myocardium and reduced peripheral vascular resistance[25,26]. Older literature reports of calcium channel blocker and combined calcium channel blocker and ß blocker ingestions, the majority of patients have received between 0.5and 2 units/kg/h insulin infusions[27]. Usual dosing includes an initial bolus of 1 unit/kg followed by a 0.5–1 unit/kg/h continuous infusion, although doses of up to 10 units/kg/h are used in refractory cases.

Insulin potentiation therapy(IPT) : Insulin is used in combination with low dose chemotherapy to avoid toxicity and chemoresistance. Insulin enhances the effects of chemotherapy, which enables 75%–90% reduction of the estimated doses of anticancer drugs thus reducing the risk of their adverse effects[28]. Therefore, insulin is used as an adjunct to low-dose chemotherapy. The mechanism of potentiation of chemotherapy is unclear. The mechanisms that were considered are as follows. Firstly, insulin increases the permeability of the cell membrane for cytotoxic drugs, resulting in higher intracellular drug concentrations. Due to the influence of insulin on cell cycle kinetics, insulin would increase the S-phase fraction of tumor cells, hence making the tumor more vulnerable for the action of cytotoxic drugs, in particular cell-cycle-phase-specific agents. Additionally, IPT would differentiate between cancerous and normal cells based on the higher levels of insulin receptors on cancerous cells[29].

Schizophrenia : Deep insulin coma therapy by insulin injection to induce severe hypoglycemic coma for 10-15minutes followed by reversal with glucose infusion was used for a few days or till patient's symptoms are abated[30]. This treatment was stopped in 1950s due to severe risk to life.

Septic shock : Hyperglycemia and insulin resistance are common in critically ill patients, independent of a history of diabetes mellitus [31]. Other reasons for hyperglycemia during critical illness include enhanced hepatic gluconeogenesis, impaired insulin secretion, and decreased insulin sensitivity due to anti-insulin effects of stress hormones, and proinflammatory cytokines have been revealed[32]. Insulin resistance seen in sepsis can be restored to normalcy by infusing insulin continuously[33]. Insulin use is shown to improve septic shock.

Aging : Insulin has also been associated with an increased release of Klotho[34]. Klotho is a recently discovered antiaging (aging suppressor) gene, and it is expressed in mouse pancreatic islets and insulinoma beta cells (MIN6 cells)[35]. In humans, the klotho levels decrease gradually with advanced age[36]. Older studies observed in that secretion of Klotho is regulated by insulin[37]. Klotho inhibits aging by interfering with the actions of insulin and insulin

growth factor 1, an evolutionarily conserved mechanism for extending life span[38]. Klotho-induced inhibition of insulin/IGF-1signaling is associated with increased resistance to oxidative stress, which potentially contributes to the anti-aging properties of klotho[37]. Overexpression of klotho protein extended the life span in mice[39]. This suggests the possibility that insulin might be involved in the processes of anti-aging and longevity. It needs further research before it can be used practically.

Conclusion:

Traditional use of insulin is for the glycemic control but it has a variety of non-diabetic uses as well. Thus, insulin has potential in assisting management of many other diseases due to its pleiotropic effects.

References

1 Martirosyan DM — Functional foods for chronic diseases: advances in the development of functional foods. USA: D & A Inc, 2008,Volume 3: 76.
2 Shafia S — Nondiabetic uses of insulin. *WJPMR* 2016, **2:** 27-30.
3 Simsek Y, Karaca Z, Tanriverdi F, Unluhizarci K, Selcuklu A, Kelestimur F — A comparison of low dose ACTH, glucagon stimulation and insulin tolerance test in patients with pituitary disorders. *Clin Endocrinol (Oxf)* 2015; **82:** 45-52.
4 Dickstein G — The assessment of the hypothalamo-pituitary-adrenal axis in pituitary disease: Are there short cuts? *J Endocrinol Invest* 2003; **26:** 25-30.
5 Sarlos S, Inder WJ — Selective use of the insulin tolerance test to diagnose hypopituitarism. *Intern Med J* 2013; **43:** 89-93.
6 Biochemical Investigations in Laboratory Medicine. Insulin tolerance test (ITT). Available at www.pathology.leedsth.nhs.uk/dnn_bilm/Investigationprotocols/Pituitaryprotocols/InsulinToleranceTest.aspx. Accessed 10 Jan 2018.
7 Melmed S, Jameson JL — Disorders of the anterior pituitary and hypothalamus, Chapter 339. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine, 18th edition. USA: *The McGraw-Hill Companies* 2012; **2:** 2880-1.
8 Salter J, Best CH — Insulin as a growth hormone. *Br Med J* 1953; **2:** 353-6.
9 Temin HM — Studies on carcinogenesis by avian sarcoma viruses: VI. Differential multiplication of uninfected and of converted cells in response to insulin. *J Cell Physiol* 1967; **69:** 377-84.
10 Hayashi I, Larner J, Sato G — Hormonal growth control of cells in culture. *Cell Dev Biol* 1978; **14:** 23-30.
11 Barnes D, Sato G — Serum-free culture: a unifying approach. *Cell* 1980; **22:** 649-55.
12 Novo Nordisk Pharmatech. Insulin human AF-Origin & application. Available at http://www.fefchemicals.com/biopharm/dataabout-insulin-human/origin-application/. Accessed on 29 Aug 2014.
13 Sodi-Pallares D, Testelli MR, Fishleder BL, Bisteni A, Medrano GA, Friedland C, *et al* — Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. *Am J Cardiol* 1962; **9:** 166-81.
14 Maroko PR, Libby P, Sobel BE, Bloor CM, Sybers HD, Shell WE, *et al* — Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation* 1972; **45:** 1160-75.
15 Marcuard SP, Dunham B, Hobbs A, Caro JF — Availability of insulin from total parenteral nutrition solutions. *JPEN J Parenter Enteral Nutr* 1990; **14:** 262-4.
16 Davis SN — Insulin, oral hypoglycemic agents and the pharmacology of the endocrine pancreas, Chapter 60. In: Goodman & Gilman's. The pharmacological basis of therapeutics, 11th ed. New York: McGraw Hill publications, 2006: 1613-45.
17 Shizgal HM, Posner B — Insulin and the efficacy of total parenteral nutrition. *Am J Clin Nutr* 1989; **50:** 1355-63.
18 Greenway SE, Filler LE, Greenway FL — Topical insulin in wound healing: a randomised, double-blind, placebo-controlled trial. *J Wound Care* 1999; **8:** 526-8.
19 Zhang XJ, Wu X, Wolf SE, Hawkins HK, Chinkes DL, Wolfe RR — Local insulin-zinc injection accelerates skin donor site wound healing. *J Surg Res* 2007; **142:** 90-6.
20 Sonksen PH — Insulin, growth hormone and sport. *J Endocrinol* 2001; **170:** 13-25.
21 Ivy JL — Muscle glycogen synthesis before and after exercise. *Sports Med* 1991; **11:** 6-19.
22 Nolte Kennedy MS — Pancreatic hormones & antidiabetic rugs, Chapter 41. In: Katzung BG, Trevor AJ, editors. Basic & clinical pharmacology, 12th ed. New York: McGraw Hill publications, 2012: 747.
23 Banadonna RC, Saccomani MP, Cobelli C, DeFronzo RA — Effect of insulin on system A amino acid transport in human skeletal muscle. *J Clin Invest* 1993; **91:** 514-21.
24 Evans PJ, Lynch RM — Insulin as a drug of abuse in bodybuilding. *Br J Sports Med* 2003; **37:** 356-7.
25 Shepherd G — Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health Syst Pharm* 2006; **63:** 1828-35.
26 Lheureux PE, Zahir S, Gris M, Derrey AS, Penaloza A — Bench-to-bedside review: hyperinsulinaemia/euglycaemia therapy in the management of overdose of calcium-channel blockers. *Crit Care* 2006; **10:** 212.
27 Shepherd G, Klein-Schwartz W — High-dose insulin therapy for calcium channel blocker overdose. *Ann Pharmacother* 2005; **39:** 923-30.
28 Ayre SG, Perez Garcia y Bellon D, Perez Garcia D — Insulin potentiation therapy: a new concept in the management of chronic degenerative disease. *Med Hypotheses* 1986; **20:** 199-210.
29 Ayre SG, Garcia y Bellon DP, Garcia DP Jr — Insulin, chemotherapy, and the mechanisms of malignancy: the design and the demise of cancer. *Med Hypotheses* 2000; **55:** 330-4.
30 Jones K — Insulin coma therapy in schizophrenia. *J R Soc Med* 2000; **93:** 147-9.
31 Das UN — Critical advances in septicemia and septic shock. *Crit Care* 2000; **4:** 290-4.
32 Lang CH, Dobrescu C — In vivo insulin resistance during nonlethal hypermatebolic sepsis.*Circ Shock* 1989; **28:** 165-78.
33 Das UN. Insulin in sepsis and septic shock. *J Assoc Physicians India* 2003; **51:** 695-700.
34 Chen CD, Podvin S, Gillespie E, Leeman SE, Abraham CR — Insulin stimulates the cleavage and release of the extracellular domain of Klotho by ADAM10 and ADAM17. *Proc Natl Acad Sci USA* 2007; **104:** 19796-801.
35 Lin Y, Sun Z — Antiaging gene klotho enhances glucose-induced insulin secretion by up-regulating plasma membrane levels of TRPV2 in MIN6-cells. *Endocrinology* 2012; **153:** 3029–39.
39 Xiao NM, Zhang YM, Zheng Q, Gu J — Klotho is a serum factor related to human aging. *Chin Med J (Engl)* 2004; **117:** 742-7.
37 Yamamoto M, Clark JD, Pastor JV, Gurnani P, Nandi A, Kurosu H, *et al* — Regulation of oxidative stress by the anti-aging hormone klotho. *J Biol Chem* 2005; **280:** 38029-34.
38 Boston University. Insulin regulates the secretion of the anti-aging hormome klotho. Science Daily, 30 November 2007. Available at www.sciencedaily.com/ releases/2007/11/071127115519.htm. Accessed 14 Mar 2014.
39 Kurosu H, Yamamoto M, Clark JD, Pastor JV, Nandi A, Gurnani P, *et al* — Suppression of aging in mice by the hormone Klotho. *Science* 2005; **309:** 1829-33.