“I cannot determine what I ought to transcribe till I am satisfied how much I ought to believe”

- Gibbon (Decline and fall of the Roman empire, Chapter XVI)

Summary
Diabetes is a metabolic disorder of carbohydrates, proteins and fat, due to relative or absolute deficiency of insulin secretion or altered receptor sensitivity. This syndrome is associated with complications viz., nephropathy, cardiomyopathy, retinopathy and gastrointestinal neuropathy. Gastrointestinal (GI) complications viz., nausea, vomiting, dysphagia, gastroparesis, diarrhoea and constipation or fecal incontinence, cause considerable morbidity in diabetic patients. It is presumed that these complications arise due to uncontrolled hyperglycemic state. Therefore, patients suffering from gastrointestinal disorders will have altered transit of food material along the tract which in turn is influenced by chronic hyperglycemia or transient hypoglycemia (drug-induced) and altered serum insulin level.

Insulin is the key hormone involved in maintenance of blood glucose homeostasis. It is prescribed as a drug of choice in the treatment of insulin dependent DM to correct hyperglycemic state. It is generally known that complications associated with DM are due to glucose toxicity. Hence, any intervention controlling elevated blood glucose level will prevent the progression of the disease and minimize the associated complications. Patients suffering from peripheral neuropathy have shown prompt improvement of painful symptoms upon treatment with subcutaneous insulin infusion. In addition, insulin was reported to induce antinociception in experimental animals through mechanisms mediated by dopamine, serotonin and opioids. The inherent analgesic response of insulin might be one of the factors involved in relief of painful neuropathy in DM patients. However, no study is available about evaluation of GI complications between untreated and insulin treated diabetes.

Streptozotocin (STZ) is frequently used as a tool to produce experimental DM in animals. However, it is reported to produce axonal neuropathic changes in autonomic NS supplying the gut and abnormalities in motor function of intestine. Hence, STZ-treated animals do not reflect the true disease condition in humans as it affect nervous system in animals. These evidence discouraged the use of STZ-model and prompted us to use normal physiological animals as they possess intact nervous system, which can reflect any alterations-induced by any treatment module. This, along with evidence cited above
led us 1) to study the effect of altered blood glucose level on SIT and *vice versa* 2) whether any relationship exists between SIT and insulin level 3) whether insulin administration produce any alteration of GI motility in normal animals.  

Food deprivation for long periods of time produced significant fall in blood glucose level in all the groups particularly hypoglycemic level was observed after 24 h of fasting. A fall in BG or hypoglycemic condition did not alter the SIT. This finding indicates fasting or hypoglycemic condition do not alter SIT. All the periods of food deprivation that produced fall in blood glucose did not show lower serum insulin level from free fed group. A surprising finding in this animal species is that hypoglycemia affected groups did not show any fall in insulin level. This indicates that insulin plays a different physiological role in fasting, in addition to its usual role.  

Fall in blood glucose level by oral hypoglycemic drug glibenclamide administration (10 mg/kg), was associated with significant acceleration of SIT. Glibenclamide significantly elevated serum insulin level. This indicates either glibenclamide *per se* accelerated SIT or indirectly through endogenous insulin or fall in blood glucose level. When compared among different periods of fasting and glibenclamide treated group, an associated downward trend is observed with BG and SIT in all the groups except 24 h fasting and glibenclamide treatment. This indicates only the drug-induced hypoglycemia is associated with acceleratory effect on SIT.  

Hyperglycemia do not affect the SIT, except the severe hyperglycemia which attenuated the SIT. This attenuation might be due to osmoceptive or anticholinergic effect of dextrose. Euglycemic state attained by intermittent dextrose administration (1 g/kg) did not affect the SIT. This indicates euglycemia and hypoglycemia attained by fasting do not alter SIT.
Blood glucose elevated by clonidine (0.1 mg/kg) is associated with attenuation of SIT and serum insulin level. Attenuation of SIT might be caused by elevated blood glucose level, lowered insulin level or direct effect of clonidine on SIT. An elevated BG level at physiological range might have only favoured attenuation of GI motility. When compared with blood glucose elevation produced by different doses of dextrose and clonidine, hyperglycemic effect *per se* has very little effect on SIT. Hence, it can be inferred that attenuation of SIT is associated with fall in serum insulin level.

Metoclopramide (5 mg/kg) had significantly accelerated SIT elevated blood glucose level without altering insulin level. Here the SIT acceleration is due to metoclopramide’s prokinetic effect on SIT. Atropine administration (1 mg/kg) produced attenuation of SIT without affecting blood glucose and serum insulin level. This attenuation of SIT was mainly attributable to atropine only, as neither BG nor serum insulin levels were altered. Acceleratory and inhibitory effects produced on SIT by metoclopramide and atropine were the individual effect of administered drugs and GI acceleratory effect may be one of factors altering the glycemic state.

Exogenous administration (s.c) of insulin did not affect the blood glucose level except the highest dose (2 U/kg). However, in all the doses insulin produced significant acceleration of SIT. The novel finding of this study is that the lowest dose of insulin (2 μU/kg) produced significant acceleration of SIT without lowering blood glucose level. Repeated administration of insulin did not produce tolerance in GI motility response indicating the sustained action of insulin on SIT.

Different doses of insulin administration produced significant elevation of serum insulin levels. The elevation is maximal with 2 mU of insulin. This elevation is not just due to exogenous insulin administration but is due to reflex secretion of endogenous insulin which was confirmed by simultaneous elevation of C-peptide of insulin level. *In vitro* insulin produced tonus in isolated longitudinal muscle of mice ileum. This is the evidence of direct myogenic effect of insulin. As the specific antagonists of insulin at its receptors are not available, it is not possible to further validate the effects of insulin.
The various mechanisms involved in acceleratory effect of insulin on SIT are via (in order of greater to lower) (1) α-adrenergic mechanism (2) cholinergic mechanism (3) Calcium channels.

Centrally administered insulin at lowest dose (2 μ U/kg) produced inhibition of SIT and the highest dose (2 U/kg) produced acceleration of SIT. Other doses of insulin did not affect the SIT. Surprisingly the peripherally administered (s.c) insulin, even at lowest dose has accelerated SIT. This indicates peripherally administered insulin exerts significant effect on SIT.

In summary, exogenously administered insulin possess stimulatory or prokinetic like action on small intestine and elevated endogenous insulin level favour the said action.