The Antidiabetic Effects of Chromium-Colchicine Combination in Human

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Abstract:
Diabetes mellitus is one of the leading causes of morbidity and mortality all over the world. Strategies of treating this disease are variably depending on the nature of diabetic pathophysiology and the drug mechanism of action and toxicity. Up to 90% of type II diabetes are attributed to amyloid fibril deposition so that the conventional insulin releaser like glibenclamide and sensitizer like metformin are no longer being curative. In this study we have assessed the method of correcting amyloid dystrophic pancreatic disorder with the alkaloid colchicine and a trial of reducing insulin resistance with the trace element chromium in combination in a course monitored with 1/2hr glucose tolerance test and ultrasonic assessment of pancreatic body thickness. A four months course of daily treatment with colchicine-chromium revealed promising curative anti-amyloid activity as compared with start of treatment and control groups at P<0.05 in that amyloid pancreatic body thickness had been reduced from 1.5 to 1.2 cm before and after treatment respectively with a cumulative increase in insulin releasing activity estimated by increasing ability to reduce blood glucose from 185 to 135 mg/dl +/- 5 with regression
coefficients $r = -0.97$ as compared to the glibenclemide-metformin $r = -0.45$ at the end of the treatment. From the overall results we concluded that treating type II diabetic patients with combined anti-amyloid and insulin sensitizer have more promising permanently curative antidiabetic effects.

**Introduction:**

Studies with the insulin-sensitizing nutrient, the trivalent chromium picolinate indicate that it aids glucose tolerance in type II diabetes, lowers elevated LDL cholesterol, reduces body fat while increasing lean mass, if it is given in a dose of (200 mcg/d) for Type 1 (IDDM) and Type 2 (NIDDM). Chromium reduces insulin, sulfonylurea or metformin requirements in patients. The success rate is greater in those with NIDDM (57.2%) than in those with IDDM (33.6%).

Recent advances in chromium nutrition strengthen the association of insufficient dietary chromium and risk factors maturity-onset diabetes and cardiovascular diseases and further document the role of chromium in the maintenance of optimal health. Because chromium is an essential trace element for normal carbohydrate metabolism and insulin sensitivity and causes a significant decrease in immunoreactive insulin from 35 pmol/l to nil level after supplementation with some changes in serum lipids furthermore, High-dose biotin synergize with chromium picolinate by inducing glucokinase expression. Niacin-bound chromium causes a significant loss of fat and sparing of muscle with no significant adverse effects from the ingestion of 600 microg of niacin-bound chromium daily over 2 months.

Chromium picolinate is a widely available nutritional supplement marketed. 200 micrograms 3 times daily as adjunctive treatment for type 2 diabetes. Supraphysiologic concentrations of chromium and other minerals with known insulin-sensitizing activity may reduce apoA-I promoter activity.

As anti-inflammatory drugs such as acetylsalicylic acid are known to partially restore insulin response to glucose, Colchicine could significantly reduce blood glucose levels, both fasting and post-prandial when given at a dose of 0.5 mg thrice a day in NIDDM patients. There were no side effects due to the therapy. This study suggests that insulin-dependent diabetes is an autoimmune disease specifically targeting the pancreatic beta cells and islet cytotoxicity of IL-1 and TNF is highly dependent on the functional state of the beta cells. This suggests that during the IDDM disease process as some beta cells are destroyed, the compensatory increased activity of the remaining beta cells may increase their susceptibility to cytokine attack.

Colchicine has anti-diabetic properties through its anti-inflammatory and anti-amyloid effects. In addition to its action on the elements of enterocytes' apical contractile complex and cytoskeleton inhibits the process of absorption of glucose and plant oil in the small intestine.

Degradation of the amyloid precursor protein (APP) by lysosomes has been proposed to be the mechanism for generation of the beta/A4 polypeptide, which is the major
constituent of amyloid plaques. Colchicine resulted in a substantial accumulation of both mature and immature APP isoforms. The inhibitor of autophagy, 3-methyladenine, had no effect on the level of APP isoforms. These results suggest that changes in ionic balance, membrane fluidity or vesicle fusion may affect APP processing.\(^{(13)}\)

Amyloidosis is a heterogeneous group of diseases characterized by extracellular accumulation of an eosinophilic, hyaline and proteinaceous material containing mucopolysaccharide substance in various tissues and organs. Knowledge about the chemical structure of amyloid fibril proteins has led to the recognition of various forms of amyloidosis including Amyloid-A (AA), Amyloid-L (AL), and hereditary, senile, dialysis-related, localized and cerebral amyloidosis. Effective supportive therapy and to control the underlying diseases by colchicine.\(^{(14)}\)

Type 2 (non-insulin-dependent) diabetes mellitus is characterized by hyperglycaemia, peripheral insulin resistance, impaired insulin secretion and pancreatic islet amyloid formation. The major constituent of islet amyloid is islet amyloid polypeptide (amylin). Islet amyloid polypeptide is synthesized by islet beta cells and co-secreted with insulin. Pharmacological doses of islet amyloid polypeptide have been shown to inhibit insulin secretion as well as insulin action on peripheral tissues (insulin resistance).\(^{(15)}\)

NIDDM is a heterogeneous disease and subgroups of NIDDM include MODY (Maturity Onset Diabetes of the Young), Malnutrition-related diabetes (MRDM) and fibrocalculus pancreatic diabetes (FCPD). Endocrine cell population is relatively unchanged in NIDDM: B-cells are reduced by up to 30% and A-cells increased by 10%. Islet amyloid is found in 96% of subjects occupying up to 80% of the islet associated with a reduction in B-cells. Amyloid formation is unlikely to cause diabetes but progressive accumulation increases the severity of the disease. Islet amyloid is formed from the islet amyloid polypeptide (IAPP), a normal constituent of B-cells, co-secreted with insulin causes fibrillogenesis whereas stimulation of B-cell secretion in NIDDM by obesity, hyperglycaemia or sulphonymurea therapy may promote amyloidosis and further aggravate islet pathology. A mutation of the glucokinase gene in MODY leads to diminished B-cell secretion but not amyloid formation. Diabetes and mutations of mitochondrial DNA is associated with poorly developed islet structure. Exocrine pancreatic size is reduced and there is evidence of sub-clinical chronic pancreatitis in NIDDM. In MRDM and FCPD, chronic pancreatitis and exocrine necrosis is associated with reduced insulin secretion. Unlike cystic fibrosis where islet amyloid is present in diabetic individuals, amyloid is absent from subjects with FCPD.\(^{(16)}\)

The diameters +/- SD of the head, body, and tail of the pancreas in IDDM patients (1.9 +/- 0.3; 0.9 +/- 0.2; and 1.4 +/- 0.2 cm, respectively) were smaller than in NIDDM patients (2.7 +/- 0.4; 1.2 +/- 0.3; and 1.8 +/- 0.4 cm, respectively) and control group subjects (2.4 +/- 0.4; 1.1 +/- 0.3; and 1.8 +/- 0.4 cm, respectively). The pancreatic shrinkage in IDDM patients was clearly evident after 10 yr of the disease. NIDDM patients and control subjects had similar pancreatic dimensions, except for a greater body thickness in NIDDM patients with > 10 yr of disease (1.2 +/- 0.4 vs. 1.1 +/- 0.3 cm).
These results were not related to differences in age, sex, and body size. Pancreas image was hypoechogenic in 72.5% of IDDM patients and hyperechogenic in 83.3% of NIDDM patients. Smaller pancreases in IDDM patients in comparison with NIDDM patients and control subjects were clearly demonstrated only after 10 yr of disease. Patients with NIDDM were not affected by pancreatic dimensions, except for a greater body thickness after 10 yr of disease. Pancreatic echogenicity increased with age.\(^{(17)}\)

**Materials and Methods:**
Five groups of type II diabetic patients had been monitored in a private clinic regarding their ½ hr glucose tolerance test and ultrasonic pancreatic body thickness estimation according to their modes of treatment. Out of the 50 patients, ten were females. The average patients’ weights were between 60-100 kg body weight and lied between 40-58 years old with 2-10 years of diabetic history.

They were divided into group 1,2,3,4 and 5 (N= 5,10,10,10,15 respectively) as a control untreated, glibenclemide treated, meformin treated, metformin-glibenclemide treated and colchicine-chromium treated groups respectively. All patients were measured for their ½ hr GTT weakly and arranged for ultrasonic pancreatic body thickness assessment (in cm) before treatment and monthly then after along 4 months as an informative method of assessing the amyloid induced thickening in most type II diabetic patient.\(^{(17)}\)

**Materials used included:**
1-The control untreated group was partially restricted with diet and not given any hypoglycemic agent.
2-Glibenclemide (Daonil tab. Cypres) alone was given in 10 mg orally daily at morning throughout the 4 months of treatment and monitoring.
3-Meformin (Glucophage tab. Kimadia) alone in 500 mg orally daily at morning and at night.
4-Glibenclemide-Metformin combination: glibenclemide 10 mg at morning and metformin 500 mg at morning and at night orally daily.
5-Colchicine-Chromium were given as follows: colchicine(colchicine-Syria) 0.25 mg plus 100 microgram of chromium (chromium- Canada) orally daily at morning for 4 months.
Results:

Figure (1): shows the glucose tolerating activity of different antidiabetic agents throughout 13 weeks of treatment.

Chromium-colchicine showed the most significant cumulative blood glucose reducing activity in comparison with glibenclemide and metformin.

Chromium-colchicine showed the most significant pancreatic thickness reducing activity in mm as compared with the start of treatment in addition to the control and oral hypoglycemic treated groups at P< 0.05.
Discussin:
Diabetes mellitus is a critical wide spreading endocrine disturbance due to its correlation with disturbed metabolism of the major fuel in the body in addition to its irreversible pathogenesis and unreliable experimental modeling as well as that preventive measures has no benefit since most of patients had complete beta-cells destruction at time of presentation, however differences between type I and type II pathophysiological mechanisms are clear in that amyloid deposition is the encountered in 90%(15,18) of the later whereas autoimmune beta-cells destruction is the major mechanism of type I diabetes. A trial to suppress autoimmune activity and amyloid deposition was carried in this study with a half strength (0.25 mg) colchicine in addition to sensitizing peripheral cells for insulin by 100 microgram single dose of the trivalent chromium. The results were compared with the standard insulin releaser, glibenclemide and the common sensitizer, metformin.

Professional ultrasonic assessment of the pancreatic body thickness before and after treatment was used in addition to assessing the ability of the pancreas to release insulin upon acute glucose challenge as ½ hr measured blood glucose in glucose tolerance test GTT in a 50 patients with type II diabetes.

There was a significant reduction of the abnormal thickness of pancreatic body in patient taking chromium-colchicine combination after 4 months of daily treatment in comparism with glibenclemide and meformin and the control group at P < 0.05 in that pancreatic body thickness had been reduced from 15 mm at start of treatment to 12 mm at the end of treatment course. This could be attributed to the reduction in amyloid deposition since colchicine is commonly used as anti-amyloid agent.(13)

Monthly assessing blood films for those patient was done to monitor any hemopoetic side effect of colchicine although it is commonly used as a safe treatment for connective tissue diseases and amyloidosis for prolonged periods and more daily dosage.(20)

Chromium alone had been repeatedly tried as a beneficial enhancer for insulin sensitization.(7)

Glucose tolerance test is considered to be more reliable parameter for assessing the ability of pancreas to secrete insulin upon challenge 75 gm of oral glucose.(19)

The combined chromium-colchicine had also showed a significant increase in pancreatic insulin release activity as reflected with ½ hour GTT with a regression coefficient r = - 0.97 as compared with r = -0.45 for the combined glibenclemide-metformin.

Although Glucose tolerance improving effect of the chromium-colchicine agreed with many studies that tried chromium alone, the cummulative improving activity is clear in this study.(6,11)

Recommendation: More antidiabetic trials are to be emphasized based on reversing the real pathphysiologic mechanism including immunemodulating effects and anti-amyloid measures in type I and type II diabetes respectively as well as using the natural hypoglycemic agents.

Reference:
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