Chronic Fluorides Impact on Pancreatic Islet Cells in Workers

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Summary: Decreasing of the insulin concentration and increasing of the C-peptide level in blood serum of 72 workers of cryolytes industries detected by radioimmunilogical method. These changes were caused by the fluorine intoxication of workers.

A characteristic symptom of chronic fluoride intoxication (CFI) is a change in the morphofunctional state of several endocrine glands: thyroid and parathyroid [1, 2, 8, 9], adrenal [1, 2, 5], sex glands [4, 6, 7].

The pancreas plays an important role in the system of neuroendocrine regulation of metabolic processes [3]. The impact mechanism of fluoride on the pancreas and in particular on its hormonal function has not been researched sufficiently [1, 2].

The aim of the present paper was to study the particularities of the pancreatic hormonal function in patients with CFI. Immunoreactive insulin (IRI), glucagon (G) and C-peptide content in blood serum of 72 male cryolite industry workers aged 30-50 (main group) and 17 men of corresponding age not affected by fluoride compounds (control group). Depending on the extent of exposure to fluoride compounds (HF, NaF, cryolite, etc.) whose concentrations in the air of working areas were usually 5-20 times above the MPC the study population was split as follows: under 10 years – 15 subjects; 11-15 years – 13; 16-20 years – 16; more than 20 years – 28. Depending on the CFI stage [5] the workers were distributed as follows: stage I – 15 subjects; stages I-II – 12, stage II – 16; there was suspicion of fluorosis (SF) in 29 subjects.

Hormones in blood serum were determined using imported and domestic radio immunology sets. Radioactivity was measured using the "Ultragamma-1280" spectrometer by LKB-Wallace (Sweden).

The men of the main group exhibited a confirmed decrease in the level of IRI in blood serum, accompanied by an increase in C-peptide (see table). Glucagon and glucose concentration in the blood serum of men in the main group did not differ from the control group.

A marked tendency was observed towards hypoinsulinemia, depending on the duration of the subjects' exposure to fluoride and CFI stage. The differences in the IRI content in the blood of workers with over 20 and less than 10 years experience were significant ($p<0.05$). The lowest IRI concentration was observed in the blood of stage II CFI patients ($p<0.001$). C-peptide, G and glucose change dynamic in the blood serum of workers, depending on the disease stage, is less pronounced. At the same time the highest concentration of G was observed in the blood of men with over 20 years experience. It was significantly different from the concentration in workers with 11-15 years ($p<0.05$) and 16-20 years ($p<0.02$) experience. The lowest C-peptide concentration was observed in the blood of stage I-II CFI patients and was significantly different from the concentration in the blood of men with SF. No clear correlations between the levels of IRI, G and glucose concentration in the blood of participating workers were observed. However the highest glucose level (5.38±0.67 μM/L) accompanied by hypoinsulinemia (43.2±7.5 μM/L) and normal G content (15.3±6/0 μM/L) was observed in stage II CFI patients.

In the main group 3 men had diabetes mellitus. They were all aged over 40, their exposure to fluoride compounds over 18 years. Of them, 2 had stage I and II fluorosis. At the time of the study the duration of diabetes was between 4 and 8 years. However in general the workers participating in the study did not have complaints related to pancreatic hormonal function disorders.

The data obtained by us indicates certain changes in the concentration of insular hormones in the blood of subjects with CFI. This is particularly true for the decrease of IRI levels, which correspond to data [12] on hypoinsulinemia in fluorosis patients. These authors observed diabetes mellitus in 4.8% of cases in a large

group of subjects of both sexes (workers at a superphosphate plant). The incidence of diabetes in the group of experienced workers at the plant was even higher – 8.5%.

Until now there is no clear explanation for the changes in pancreatic hormonal function during CFI. There is data on direct inhibiting impact of fluoride on insulin synthesis [11] expressed as decreased inclusion of L-[4.5 H3]-leucine into proinsulin and insulin under the influence of various sodium fluoride concentrations on Langerhans islets in rats. It was also shown that insulin secretion depended less on the impact of fluoride than on the hormone's biosynthesis. The toxic impact of fluoride on insulin biosynthesis was not decreased by adding glucose or pyruvate. Microcirculatory defects, increased capillary permeability and an indication of protein biosynthesis in the pancreas [1, 10] may also be the reason for a decrease in the pancreatic hormonal function with this pathology.

Blood insulin level is determined not only by the speed of its production or secretion, but also by the dynamic of the hormone's metabolic degrading that occurs, mainly, in the liver. Therefore, during an analysis of possible reasons for the decrease of IRI in the blood, it seems necessary to take into account any possible disruptions in the functioning of this organ. Patients with fluorosis with symptoms of toxic hepatitis have exhibited a confirmed decrease in IRI contents in blood compared to workers in the main group without disruptions in the functioning of the liver (64.0±9.3 and 103.3±14.7 pM/L; $p<0.05$). The levels of G and C-peptide in the blood of men in both groups were practically the same (12.30±2.50 pM/L and 0.90±0.13 nM/L correspondingly, with toxic hepatitis; 15.70±2.8 pM/L and 1.12±0.16 nM/L correspondingly without toxic hepatitis). The C-peptide/IRI ratio, which is an indirect but reliable indicator of insulin extraction in the liver, was higher in CFI patients with toxic hepatitis symptoms than in subjects without indications of liver damage (12.7±1.6 and 8.1±1.5; $p<0.05$). Consequently, without rejecting the above factors explaining the disruption of the pancreatic hormonal function by the direct impact of a toxic agent on certain Langerhans islets

Table 1 - Insulin, G, C-peptide and glucose contents in blood serum of men in the main and control groups (M±m)

Group	Insulin μM/L	G μM/L	C-peptide μM/L	Glucose μM/L
Main (*n*=72)	82.15±7.4	14.00±1.65	1.00±0.10	1.00±0.10
Control (*n*=17)	113.30±10.9*	13.40±3.50	0.45±0.10*	4.70±0.20
Workers' experience				
under 10 years (*n*=15)	121.10±18.90	15.70±4.80	1.15±0.20	4.70±0.20
11-15 years (*n*=13)	78.90±17.20	9.40±3.25	0.95±0.30	5.00±0.60
16-20 years (*n*=16)	81.10±20.10	9.60±1.80	1.05±0.90	4.65±0.35
over 20 years (*n*=28)	68.20±9.30*	18.80±3.00*	0.90±0.20	4.70±0.20
Subjects at CFI stage				
SF (*n*=29)	102.60±15.10	9.50±1.85	1.20±0.15	4.30±0.40
I (*n*=15)	88.25±14.35	17.50±7.20	0.95±0.50	4.65±0.10
I - II (*n*=12)	62.00±10.80*	10.65±3.00*	0.60±0.10	4.85±0.30
II (*n*=16)	43.20±7.50*	15.30±6.00	0.85±0.40	5.38±0.67

Note: * denotes values that are significantly different from the control group ($p<0.05$); *n* is the number of observations

structures, it may be considered that hypoinsulinemia during CFI may be secondary reflecting the particularities of this hormone's metabolism in the liver of fluorosis patients.

Thus the analysis of the results obtained and secondary data allow us to conclude that the pancreas is not unaffected during CFI. For the first time we have provided a complex characteristic of insulin, G and C-peptide contents in the blood serum of people during CFI, which evidenced moderate hypoinsulinemia accompanied by normal or slightly elevated G and glucose levels. Hormonal status changes reflect the complex mechanism of direct or indirect fluoride impact on the production and metabolism of insular hormones. The dynamic of lowering insulin concentration in the blood of fluorosis patients, depending on the intoxication stage, accompanied by a tendency for hypoglycemia, requires more detailed attention, since modern interpretations dictate that absolute or relative insulin deficiency determines the development of diabetes mellitus, triggers disruptions in carbohydrate, fat and protein exchanges and liver function [3]. Further clinical lab and hormonal studies should more fully evaluate the role of the pancreas in CFI pathogenesis and of fluoride as a diabetes-inducing factor.

Conclusions. 1. Cryolite industry workers exhibit moderate hypoinsulinemia accompanied by normal G levels and a verifiable C-peptide concentration increase.

2. A tendency was discovered for insulin levels to decrease depending on the duration of exposure of workers to fluoride compounds at the CFI stage.

3. Changes in the hormonal state reflect the complex mechanism of direct or indirect fluorides impact on the production and metabolism of insular hormones.

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Received: February 19, 1991.

*Translated from Chinese into English by **TransPerfect Translations International, Inc.**, courtesy of the Fluoride Action Network (2012). For more translations of Chinese research on fluoride toxicity, see www.fluoridealert.org/researchers/translations/*