Polish J. of Environ. Stud. Vol. 18, No. 2 (2009), 273-277

Original Research

Relations between Iron Deficiency Anemia and Serum Levels of Copper, Zinc, Cadmium and Lead

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Received: 30 January 2008
Accepted: 4 August 2008

Abstract

Iron deficiency anemia (IDA) is a common nutritional deficiency syndrome. Lead and cadmium are major hazard elements to humans in industrialized countries. Zinc and copper are essential and play important roles in different physiologic and pathologic conditions. The aim of our study was to determine levels of serum Cu, Zn, Fe, Cd and Pb in IDA patients, and to investigate the relationship between these elements and IDA.

This study was performed on 141 adults (age 18-40 years) living in the Denizli region of Turkey. Iron deficiency anemia was observed in 81 individuals; 60 healthy persons (without anemia) were regarded as controls. Blood samples were collected from subjects into without anticoagulant tubes free from Fe, Cu, Zn, Cd, Pb and sera were obtained. Element levels of serum were determined using an atomic absorption spectrophotometer. The study took place in the Pamukkale University Faculty of Medicine in 2005.

The levels of lead in serum were significantly ($p<0.001$) higher in adults with IDA than controls. Serum copper and zinc concentration of the IDA group were not found to significantly ($p>0.05$) differ from the control group. Cadmium level in IDA group appeared to be higher than control, but not significantly ($p>0.05$) different from that of the control group. Hemoglobin, mean corpuscular volume, red blood cell, ferritin and iron levels in subjects with IDA were significantly ($p<0.001$) lower than control.

Serum lead concentration is high in IDA subjects versus healthy individuals. So it can be said that lead exposure may be a risk factor for the occurrence of iron deficiency anemia in humans. In addition, it can be said that iron deficiency may increase susceptibility to lead poisoning because it has been speculated that iron deficiency can cause increased absorption of lead.

Keywords: iron deficiency anemia, copper, zinc, cadmium, lead, iron

Introduction

Levels of heavy metals in air, water and soils have increased in recent years, both in urban and periurban areas [1]. In terms of potential adverse effects on animal and human health, cadmium (Cd), lead (Pb) and arsenic are amongst those elements that have caused the most concern. Pb is considered to be one of the major environmental pollutants and Pb poisoning is an important problem in humans [2]. Iron (Fe) plays an essential role in many biological processes, and it is important to maintain Fe concentration within its normal narrow range [3]. The physiologial

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Table 1. The comparison of hematological parameters between groups (M±SE).

	Iron Deficiency Anemia Group			Control Group		
	Total (n=81)	Female (n=53)	Male (n=28)	Total (n=60)	Female (n=39)	Male (n=21)
Hb (g/dl)	9.75±0.24	9.84±0.29	9.57±0.42	14.79±0.18*	14.70±0.25	14.83±0.23
MCV (μ^3)	73.20±1.74	71.60±2.10	75.94±3.00	85.36±1.16*	85.14±1.69	85.74±1.11
RBC ($x10^6/mm^3$)	4.21±0.08	4.26±0.08	4.11±0.18	4.99±0.06*	4.97±0.07	5.02±0.10
Ferritin (ng/ml)	5.72±0.59	5.63±0.72	5.86±1.04	32.93±1.74*	32.06±1.89	34.54±3.56

* Shows significance between control and iron deficiency anemia (IDA) groups. Significance between groups were evaluated by Independent-samples T, * $p<0.001$.

function of Fe is to participate in oxidation-reduction reactions that take place in the process of electron transfer of the respiratory chain. Iron deficiency is a serious health problem that affects a great part of the world's population, especially in developing countries [4].

The biological role of trace elements, especially zinc (Zn) and copper (Cu), in different physiologic and pathologic conditions has been extensively investigated in recent years. Zn, a constituent of more than 200 enzymes, plays an important role in nucleic acid metabolism, cell replication, tissue repair and growth through its function in nucleic acid polymerases [5]. Cu is an essential nutrient that is widely distributed in food and water and a component of several metalloenzymes that are required for oxidative metabolism, including cytochrome oxidases, ferroxidases, amino oxidases, superoxide dismutase, ascorbic acid oxidase and tyrosinase [6].

Cd is a nonessential element that has raised concern recently due to its accumulation in the environment as a result of industrial and agricultural practices [7]. The points at which pollution is most apt to occur begin with mining and smelting, followed by manufacturing, loss from manufactured products during use and when discarded, and the reclamation and use of waste products contaminated with Cd. Pb, as an environmental contaminant, is often used as a chemical complex with Cd, which has effects similar to those of Pb so that their effects are additive [8, 9].

Pb is recognized as one of the most important heavy metal contaminants in the environment. Tandon et al. showed that Cd and Pb could induce changes in the metabolism of essential metals like Zn, Fe and Cu [10]. In addition, the use of Cd and Pb in rats showed no difference when they were used combined and alone in terms of changes in the serum levels of essential metals such as Zn, Cu and Fe [11]. Some studies have shown that iron deficiency predisposes individuals to increased gastrointestinal lead absorption [12, 13]. Although the association between iron deficiency and lead has been investigated in a number of studies, results remain inconsistent. According to a large review on the interactions between IDA and Pb, some studies show a positive association whereas others show no association [14-17]. A recent study has shown no statistically significant difference in blood levels of Pb between anemic children and controls. But, significantly negative correlation had been found between Pb and hemoglobin levels in anemic children in the same study [18].

The aim of the present study was to investigate the content of Cu, Zn, Cd and Pb in the serum of adults with IDA in the Denizli province of Turkey.

Methods

This research was performed on 81 subjects with IDA (female n=53 male n=28) aged 18 to 40 years and 60 healthy adults (female n=39 male n=21) as controls aged 18 to 40 years old living in Denizli city center, which was a heavily polluted area in 2005. Volunteer subjects were included in the study. IDA was defined as a hemoglobin concentration of 11 g/dl or less with a low serum ferritin level (<10 ng/dL) [19] in the Pamukkale University Faculty of Medicine. The patients had no additional disease known except for IDA. Controls were chosen among relatives of the patients. All subjects were informed about the study and written informed consent was obtained. The Pamukkale University Ethics Committee approved the study (Turkey).

Blood samples were obtained from all subjects and divided into two, one for the red blood cell (RBC), hemoglobin (Hb) mean corpuscular volume (MCV) in CBC tubes, one for the ferritin and element levels in tubes without anticoagulants. The samples were collected in the internal disease clinic. Numbers of RBC, Hb and MCV of whole blood samples were measured with an automatic cell counter (Coulter SKTS, Beckman Coulter, USA). Serum was separated by centrifuge and then serum ferritin levels of the all subjects was determined by chemiluminescence method using an immunanalyzer (Immulite One, Bio DPC, CA, USA). In addition, for studying serum iron, zinc blood samples were collected from subjects into non-heparinized tubes free from Fe, Cu, Zn, Cd, Pb and sera. The serum samples were preserved at -20ºC until analyzed. For the analyses of elements in blood, standard solutions were prepared using Fe, Cu, Zn, Cd and Pb standards (Merck). Deionized distilled water was used as blank. Blank and standard solutions were used for the calibration of an atomic absorption spectrophotometer [20]. The concentrations of Fe, Cu and Zn in serum were measured with a flame atomic absorption spectrophotometer (Perkin Elmer AAS-700 Ueberlingen, Germany). Serum concentrations of cadmium and lead were determined with an atomic absorption spectrophotometer with an HGA graphite furnace (Perkin Elmer AAS-700 Ueberlingen, Germany).

Results were evaluated with Student T-test and Pearson Correlation tests for significance between groups. Statistical analysis was conducted with software package SPSS 10.0 (Statistical Package for Social Sciences). Mann-Whitney U test was used for comparisons within groups, between males and females of IDA and control groups. The non-parametric test was chosen because the number of subjects was under 30. Results were expressed as the mean ±S.E. P values of less than 0.05 were considered significant.

Results

We compared Hb, MCV, RBC and ferritin values of subjects between all groups and these values differed significantly ($p<0.001$) between the control and IDA groups (Table 1). IDA was defined as a hemoglobin concentration of 11 g/dl or less with a low serum ferritin level (<10 ng/dL). In this study, when the parameters of IDA were compared to controls, we observed a significant ($p<0.001$) decline in the Hb, MCV, RBC and ferritin levels of the IDA group compared to controls.

When we compare the results of serum element levels of controls with those of the IDA group, the mean serum Zn levels were not found to be significantly different between these groups (Fig. 1). Likewise, no significant ($p>0.05$) difference was seen in the serum Cu levels between IDA and control groups (Fig. 1). The mean serum Fe levels of IDA and control groups were compared and the mean serum Fe levels in the IDA group were significantly ($p<0.001$) lower than those of control (Fig. 1). When comparing the results of serum Cd levels in IDA and control groups, we didn't observe significant differences between the serum Cd values of IDA and control subjects (Fig. 2). The serum Pb level between the control and IDA groups was compared in the present study, and the level of Pb in the IDA group was found to be significantly ($p<0.001$) increased compared to control (Fig. 3).

We observed a negative correlation between serum level of iron and serum lead value ($r = -201$, $p<0.05$). Similarly there is a negative correlation between Hb level and serum lead concentration ($r = -330$, $p<0.01$). Our results show that there is a negative correlation between serum level of iron and serum cadmium value, but it is not significant. Also, there is a negative correlation between serum ferritin and lead, and serum ferritin and cadmium, but the negative correlation was not found to be statistically significant. We did not observe significant correlation between the serum level of zinc and lead as well as cadmium.

In the IDA group, Hb, MCV, RBC and Ferritin levels of subjects were compared between female and male individuals (Table 1). No significant difference was seen in Hb, MCV, RBC, and Ferritin levels between genders in IDA groups. Also, in the control group, Hb, MCV, RBC and Ferritin levels of subjects were compared between female and male individuals. These parameter values of females were not significantly different from males in control (Table 1).

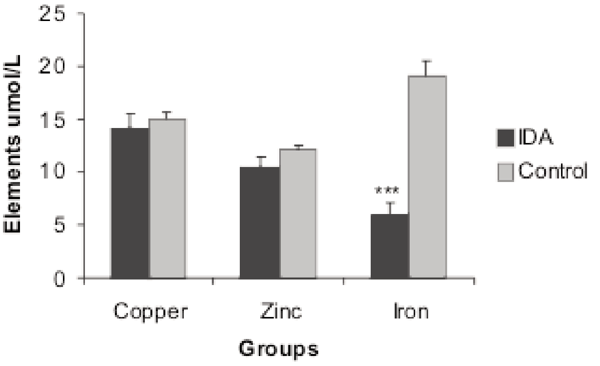

Fig. 1. The serum copper, zinc and iron levels in groups.
***Shows significance between control and IDA group. Significance between groups were evaluated by Independent samples T-test, *** $p<0.001$. Values are expressed means±S.E.

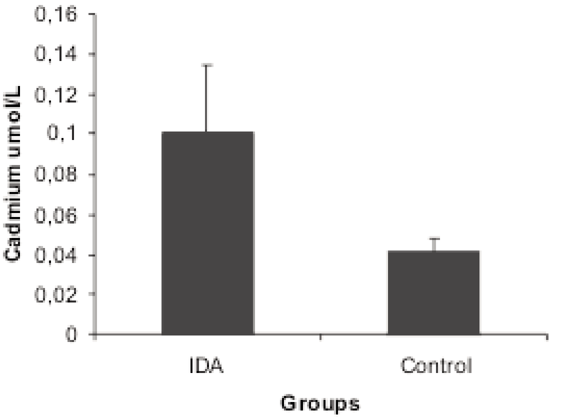

Fig. 2. The serum cadmium levels in groups. Significance between groups was evaluated by Independent samples T-test. Values are expressed means±S.E.

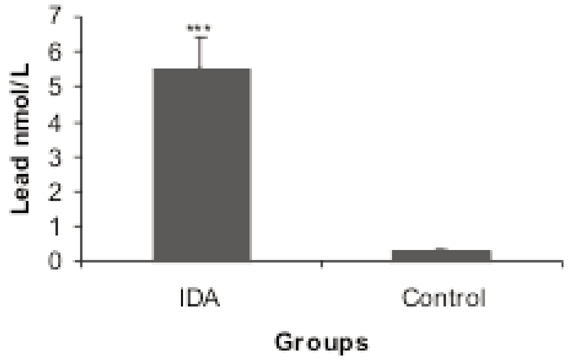

Fig. 3. The serum lead levels in groups.
***Shows significance between control and IDA group. Significance between groups was evaluated by Independent samples T-test. *** $p<0.001$. Values are expressed means±S.E.

Discussion

Iron deficiency is one of the most common causes of anemia worldwide, and is a leading nutritional cause of anemia [21]. Hemoglobin is the accepted indicator of anemia, and ferritin serum is the most-used indicator of iron deficiency. In this study, IDA was diagnosed by an internal diseases clinic to take the basis of the value of Hb, MCV, RBC and ferritin. These parameters were found to be significantly lower in subjects with IDA compared to those of the controls (Table 1). In addition, the serum level of iron in control subjects is significantly higher than IDA (Fig. 1). At the same time, we compared haematological parameters between female and male subjects within the same group. We did not observe any significant difference between genders within the group (Table 1).

Deficiency of some trace elements generally causes hypochromic microcytic anemia [21]. Serum Cu and Zn concentrations did not differ significantly between the anemic and control groups in this study (Fig. 1).

Deficiency or excess of a trace element may cause disorders in the absorption, distribution, metabolism and elimination of other trace elements. For example, iron deficiency can increase absorption of lead and cadmium from the gastrointestinal tract [22, 23]. According to some studies on the interactions between IDA and lead, a positive association was found, i.e. as the serum Pb level elevated, frequency of IDA occurrence increased. Others showed no association [14-17]. Serum lead concentration in subjects with IDA was found to be significantly higher compared to the control group. Therefore, these results show that a relationship may exist between iron deficiency and high lead levels. We also observed a negative correlation between serum level of iron and serum lead value ($r = -201$, $p<0.05$).

Similarly, there is a negative correlation between Hb level and serum lead concentration ($r = -330$, $p<0.01$). According to our results, the serum Pb levels increased while serum iron levels and Hb concentration decreased. Lead is also a problem among young children in some developing countries where exposure may be high due to continued use of lead in gasoline, urbanization, and industrial pollution [24]. Three physiological processes are proposed for the relationship between IDA and lead. First, low iron causes high expression of divalent metal transporter 1 in duodenum [12, 13]. High divalent metal transporter 1 causes a significant increase in lead absorption [13, 24]. Second, high levels of lead absorption reduce ertyhropoiesis and cause low hemoglobin levels [24]. Third, increased lead absorption in blood reduces erythrocyte survival [24]. So industrial pollution, lead dust exposure, and use of leaded gasoline may create anemia in urban communities. In addition, we can say that high levels of lead may aggravate anemia in those with IDA.

We found a high cadmium level in serum of iron deficiency group compared to control. But this increase was not statistically significant (Fig. 2). In this study, serum Fe and Zn levels were low, while Cd levels elevated insignificantly. And no significant correlation was seen between serum Cd levels and these elements. The reason for the insignificance of our results may be the large variance in Cd levels of IDA patients. Previous studies have demonstrated that lead and cadmium can interact with gastrointestinal absorption of calcium, iron and zinc. This interaction with divalent cations is considered one of the molecular bases for the toxicity of these heavy metals. The replacement of zinc in numerous enzymes and the decrease in the availability of iron could be a mechanism by which lead and cadmium exert their toxic effects, as is the case of the anemia associated with their poisoning [25]. The intestinal absorption of cadmium was found to be increased whenever total body iron was depleted [26]. The mechanism of absorption of cadmium in the gastrointestinal tract is unknown, and it is also not clear why and how iron deficiency increases cadmium absorption in the intestine [27]. A recent report has indicated that the cadmium concentrations of blood in adults 20 years or older could be 0.5 μg/L [28]. A new report has shown that urine Cd levels as low as 1 microgram per gram of creatinine may be associated with subtle kidney injury and an increased risk for low bone mineral density [29]. The report shows that about 5 percent of the U.S. population aged 20 years and older had urinary Cd at or near these levels. In our study, cadmium levels were relatively high, both in the anemia and control groups. Our subjects live in an industrial city (Denizli) that has heavy air pollution. There are many textile and other factories that cause environmental contamination. Reasons for the high cadmium concentrations may be high air pollution and industrial pollution.

We could not analyze serum metal levels before the occurrence of IDA in the patient group. It could be more striking if we managed levels of Cd and Pb in subjects. Another restricting factor for the evaluation of results was lack of determination of Cd and Pb levels in the polluted air.

In conclusion, serum lead concentration was significantly higher in IDA group than in controls. Cadmium levels in serum were found to be quite high in all subjects. Our results belong to a small number of the population, and this investigation is only a preliminary study. In view of these results, we can say that Cd and Pb, especially the latter, may be important risk factors for the formation of IDA. The reason may be environmental pollution, and exposure to heavy metal is an important problem for health in industrialized cities like Denizli. In addition, according to results reported by previous studies, it can be said that IDA may be responsible for the increased lead exposure. We are planning further epidemiological studies in a larger population to investigate the relationship among high lead and/or cadmium exposure, iron deficiency anemia and environmental pollution.

Acknowledgments

This study was supported by the Pamukkale University Research Fund (Project No. 2002TPF008).

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