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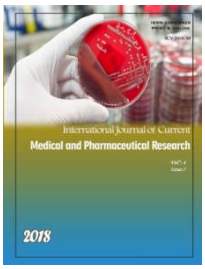

TOXICITY OF CADMIUM AS AN ENDORINE DISRUPTOR CHEMICAL ON RISK OF DIABETES MELLITUS

Sharul Rizan Ilias and Mohd Hasni Ja'afar

Department of Community Health, Faculty of Medicine, UKM Malaysia

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ABSTRACT

Various countries had a concern on the effect of cadmium towards human health. Many researches and regulations have been implemented to control expose of cadmium from the environment or man-made source. Cadmium is known to have various impacts on health, especially diabetes mellitus, hypertension and peripheral vascular disease. Not many studies on the effect of cadmium on non-communicable disease particularly diabetes mellitus. Nearly 3.5 million of Malaysian had DM that can contribute to high morbidity and mortality. This review focuses on effect of cadmium towards DM to increase awareness of the public as well as stakeholders. Contribution and active programme from all stakeholders are necessary in the prevention and control of cadmium toxicity.

INTRODUCTION

It is a challenging to control and reduce the prevalence of non-communicable disease, especially diabetes mellitus (DM) in Malaysia. Majority of Malaysian states show an increasing trend for prevalence of DM from 2011 to 2015 in National Health Morbidity Survey (NHMS) by the Ministry of Health, Malaysia (NHMS, 2011 & 2015).

DM can increase the burden of disease and put as financial health constraints to the government. Even though many research and intervention down from the policy level to the community level, the growing prevalence of DM is still the main public health issue. DM is a multifactorial disease that includes factors like sedentary lifestyle, unhealthy diet, lack of physical activity, smoking and take alcohol drinks (Hayati K.S. *et al.,*2014).

Agency for Toxic Substance and Registry (ATSDR) consider cadmium (Cd) as one of the Endocrine Disrupting Chemical (EDC). It's showed that Cd is a diabetogenic agent with various mechanisms of action (ATSDR, 2012). Some findings suggest that Cd is a risk factor for DM (Borne *et al.,* 2014; Liu *et al.,* 2016; Tseng, 2013).

Cadmium, from environment to food

Cd is a well-known useful heavy metal worldwide. It is a soft, silver-white metal, which can be found naturally in soil. It's widely used in nickel-cadmium rechargeable batteries and electroplating. Unfortunately, it's also one of the most important notorious toxic heavy metals, which is widespread in industrial and environmental pollution.

The metal can easily enter the human food chain at all levels from contaminated soils, crops and vegetables. Many researches proved that Cd could accumulate in kidney, liver, lung, pancreas and reproductive tissues and causes serious health damage. Regardless of exposure routes, Cd is found higher in the kidney. It is excreted very slowly with a half life of more than 26 years, which make it easily accumulate in the human body (ATSDR, 2012).

Cadmium, in Malaysia

Recently there are few studies showed that Perlis, a state in the north of peninsular Malaysia, had high levels of cadmium from various resources such as rice and soil. Result showed Cd concentration had exceeded allowable limits in all study sites. Types of human activities are highly influenced the level of Cd in the environment such as paddy field. Cd in the soil and the environment can be absorbed easily by plants, animals and then accumulated in the human body through multilevel of the food chain. Food crops grown on polluted soils or on soils naturally rich in Cd constitute the major source of dietary exposure. Activities include cement industry, chemical plant, quarry, mechanic workshop, wet market and heavy traffic from main roads (Nor Wahidatul Azura Zainon Najib *et al.,* 2012; Rabah S. Shareef *et al.,* 2015; Siti Norbaya Mat Ripin *et al.,* 2014). River basin area is also considered as one part of area, which poses high risk exposure to high level of heavy metals. Fadzilah *et al.,* (2014) found elevated level of certain metals in

Corresponding author:* **Sharul Rizan Ilias
Department of Community Health, Faculty of Medicine, UKM Malaysia

the upstream area of river basin of Perlis. These may be originated from fishing boats and from agriculture activity that use pesticides and possibly from the natural geological activity. Seafood also considered as one of the primary sources of heavy metals in human. In accordance to that, heavy metal levels in seafood are being monitored in Malaysia under Food Regulation 1985 (Attorney General, 2012).

Cadmium, elsewhere

Cd is widely dispersed in the environment and can enter the food chain at all levels through use of phosphate fertilizer and herbicide. The plant grew had high levels of Cd and become a threat to human and animal (Rabah S. Shareef *et al.,* 2015).

Bangladeshi population had high intake of Cd due to high intake of rice that grows in contaminated area of cadmium. The mean of Cd levels in Bangladeshi rice was 37.2 μg/kg. Fertilizer uses especially phosphate-based fertilizers are the main reason of this toxicity. Triple Super Phosphate is widely applied in rice production in Bangladesh. These urea and phosphate-based fertilizers contain high levels of Cd and other heavy metals. Urea based fertilizers also have been used for whitening puffed rice to increase it's colour for attraction of consumers (Al-Rmalli *et al.,* 2012).

Study in Jamaican showed cadmium concentrations is nearly 20 times higher due to high concentrations of Cd in crops grown on bauxite soils. However, cadmium concentrations in each crop can vary widely. Root crops (excluding root vegetables) have concentrations between 0.004 and 6.5mg kg, root vegetables from 0.001 to 1.8 mg kg−1 and green leafy vegetables ranged from 0.002–1.7mg kg (Lalor 2008). These studies confirm the significant uptake of Cd by some foods and show that low-cadmium products can be produced by judicious land use selection; a technically simple solution to meeting standard regulations related Cd.

In certain parts of Thailand, shellfish contribute major sources of Cd. Due to popular type of diet such as Blood Cockles, the exposure to Cd can be greater than provisional tolerable intake (Chunhabundit, 2016).

In Belgium, industrial areas for non-ferrous metal processing have high levels of Cd. A study found that adult population in this contaminated area had a dietary intake of Cd of almost twice compare than the general population of Belgium. The route of exposure is through ingestion of contaminated vegetables, fruits, potatoes, meat and animal offal (Vromman *et al.,* 2008).

Legislation

International Agency for Research on Cancer (IARC) classify Cd as carcinogenic to human (Group 1) and Environment Protection Agency (EPA) classified as a probable human carcinogen by inhalation (Group 1B) for lung cancer. Joint Expert Committee FAO (WHO Expert Committee on Food Additives) established the provisional tolerable intake for Cd of 25 mg/kg body weight per month (World Health Organization, 2011). This level has been widely used as health-based guidance to monitor Cd present in the human diet.

Aware of this health impact, Malaysia include various heavy metals including Cd for monitoring their Maximum Permitted Proportion under Table 1, Fourteen Schedule, Regulation 38 (Attorney General 2012).

Cadmium, effect on Diabetes Mellitus

Cd itself had a variety of health impact which include diabetes mellitus, hypertension, urinary stone, lung cancer, prostate cancer and low birth weight. Malaysia is part of the endemic country for DM which is growing exponentially for the past 5 years. DM is a common metabolic disorder, which is diagnosed with fasting hyperglycaemia and its associated symptoms such as polyuria, polyphagia, polydypsia and nocturia. DM can be due to deficiency of insulin secretion (Type 1 DM) or insulin receptor insensitivity (Type 2 DM).

DM is related with low insulin secretion and/or present of insulin resistance. Study among Japanese show a destruction of Islet β-cell due to increase oxidative stress related to tissue damage, thus leads to development of DM (Sakuraba *et al.,* 2002).

Result from Malmo Diet study also showed blood Cd is associated with a haemoglobin A1c (HbA1c) but there was no significant relationship between Cd and blood glucose level and serum insulin. Available data suggest that Cd can accumulate in red blood cells and increase HbA1c due to higher concentration of Cd in smokers rather than non-smokers (Fagerberg *et al.,* 2015). Study in Pakistan show increased level of Cd and decreased level other essentials elements are associated with DM. Their finding clearly demonstrated concentrations of Cadmium is high in scalp hair of diabetic patient as compare to reference and is not only involve active smoker but also a passive smoker (Afridi *et al.,* 2013).

A cellular studies show that Cd can accumulate in pancreatic beta cells and cause beta cell dysfunction, but also that it inhibits insulin secretion (El Muayed *et al.,* 2012). Other studies show that Cd can decrease beta cell viability and even induce beta cell death (Chang *et al.,* 2013).

An animal study with Cd exposure resulted in an increased percentage of HbA1c, as well as reduction of fasting serum insulin. Edward & Prozialeck found dose-dependent with the decrease of gene mRVA levels in pancreas of rats that exposure to Cd. Even after 12 weeks after exposure, Cd still present in pancreatic cells compare than the control group. This suggests that Cd also can accumulate in pancreatic cells and cause direct toxicity towards pancreas. Under microscopic examination, they found the α-cells and β-cells have separated from each other in Cd exposure group which does not occur in the control group. The affected cell shape is irregular and loss of cell body volume with infiltration of Red blood cell in the area of Islets of Langerhans. These evidences showed massive disruption of pancreatic cell morphology and altered cell adhesion for normal function (Edwards & Prozialeck, 2009).
These epidemiological and cellular studies indicate Cd may exacerbate or play a role in pathogenesis of DM. However, due to numerous other confounding factors inherent in these studies, it is difficult to firmly establish any cause and effect relationships. For example, other environmental toxins such as lead and arsenic also can induce DM in another study *(Afridi et al.,* 2013; Shapiro *et al.,* 2015; Yang *et al.,* 2015).

CONCLUSION

Until today, there are only a few reports investigating the relationship between cadmium pollution and diabetes occurrence in Malaysia. Additional epidemiological and cellular studies are needed to rule out the effects of such confounding variables on the possible link between dietary Cd

and diabetes mellitus. Exposure towards Cd can be varied dependent on geography and sociocultural factor. Most of the route exposures are through oral via Cd-expose foods. The Long half life of Cd in various storage and target organ could potentially affect human health. There is a strong association from many studies between Cd and diabetes mellitus. However, we need further epidemiological, cellular and toxicology study in Malaysia to confirm this association and ensure protection of Malaysian consumer from Cd exposure.

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