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RESEARCH ARTICLE

CADMIUM AS A HIDDEN DIABETOGENIC AGENT IN MALAYSIA

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ABSTRACT

Cadmium is among heavy metals that known to disrupt the human endocrine system. Its tendency to accumulate in certain organs like the liver, kidney, adrenal gland, thyroid and pancreas is believed leads to its health impacts. Many countries have implemented control on the expose of this heavy metal, either from the environment or anthropogenic sources. In Malaysia, the people are exposed through several pathways especially through food about 53.0%. Some areas have shown to have high levels of cadmium. And about 17.5% of Malaysian had diabetes mellitus that contribute to high morbidity and mortality in the country. Studies about the relationship between cadmium and non-communicable disease, particularly diabetes mellitus are very scanty. This review focuses on effect of cadmium towards diabetes mellitus to increase awareness of the public as well as clinicians. Contribution and active programme from all stakeholders are necessary for the prevention and control of cadmium endocrine toxicity.

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INTRODUCTION

The Agency for Toxic Substance and Registry has identified cadmium (Cd) as one of important Endocrine Disrupting Chemical (EDC). Various studies showed that Cd is a diabetogenic agent with various mechanisms of actions, which suggest it is one of the risk factors for diabetes mellitus (DM) (Borne *et al.* 2014; Liu *et al.* 2016). Cd is known as one of toxic metal that may easily enter the food chain at all levels from contaminated soils to crops and vegetables. Regardless of exposure routes, Cd is widely distributed in the body with the highest concentration found in liver and kidneys. The absorbed Cd is excreted very slowly with half life of more than 26 years, make it easily accumulate in any human body (ATSDR 2012).

Cadmium Exposure in Malaysia

In Malaysia, most of cadmium exposures are through food ingestion (Moon *et al.* 1996). And about 53.0% of the exposures are from rice consumption. Other studies also showed high levels of Cd in various resources such as in soil (Nor *et al*. 2012) and rice (Rabaah *et al.* 2015), that exceeded the allowable limit. Other potential ingestion sources in Malaysia are vegetables, fruits, potatoes, meat and offal (Vromman *et al.* 2008), use of urea based fertilisers for whitening puffed rice (Al-Rmalli *et al.* 2012), crops grown on bauxite soils (Lalor 2008), use of phosphate fertilizer and herbicide (Fadzilah *et al.* 2014; Rabah *et al.* 2015), and eat seafoods like blood cockles (Chunhabundit 2016). Seafoods are considered as one of the primary sources of Cd for Malaysian (Hossen *et al.* 2017). The study found the Cd concentrations in the local blood cockles was double of the limit. In view of that, Cd level in seafood is being monitored under the Food Regulation 1985 (Attorney General 2012). The regulation adopted 1.0 µg of Cd per dry weight of food as the safe limit. The Joint Expert Committee FAO (WHO Expert Committee on Food Additives) established the Provisional Tolerable Monthly Intake (PTMI) for Cd intake of 25.0 mg/kg body weight (World Health Organization 2011). River basin is also considered as part of the area with high risk exposure to Cd. A study by Fadzilah found elevated level of metals mostly at the upstream area of the river basin (Fadzilah *et al*. 2014). The condition may be contributed by oil from fishing boats, contamination from agriculture activity that use pesticides and possibly from the natural geological activity. Other activities related are emission and effluent from cement industry, chemical industry, quarry, mechanic workshop, wet market and heavy traffic from main roads (Siti Norbaya *et al*. 2014).

Diabetes Mellitus and Cadmium: Malaysia is one example of endemic country for diabetes mellitus (DM) in which the prevalence has grown exponentially for the past five years. DM

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is a metabolic disorder that diagnosed with fasting hyperglycaemia tests and it is associated with symptoms such as polyuria, polyphagia, polydypsia and nocturia. DM is due to either deficiency of insulin secretion (Type 1 DM) or insulin receptor insensitivity (Type 2 DM). It is a hard challenge to reduce the prevalence of DM in this country. Yet, there was an increasing trend from 2011 (15.2%) to 2015 (17.5%) revealed by the National Health Morbidity Survey conducted by the Ministry of Health, Malaysia (NHMS 2011; NHMS 2015). DM augments any individual burden of life and put a financial health constraints to the government. The prevalence was found higher in urban (17.7%) compared to rural (16.7%) regions. This may associated with poor urban household, which contributes to malnutrition and unhealthy diet that later worsen the pancreas health. One patient who follows up at any government health centre is estimated to incur about RM459 (USD112) every year (Feisul *et al.* 2017). Even though many researches and intervention programs were carried out from the national to community level, the growing number of new cases of DM has still remained as a public health issue in Malaysia. It is multifactorial disease that include sedentary life style, unhealthy diet, lack of physical activity, smoking and alcoholic (Afridi *et al.* 2013). Study among Japanese showed a destruction of Islet β-cell due to increase oxidative stress related with tissue damage thus leads to development of DM (Sakuraba *et al.* 2002).

Cd is among heavy metals that leads to cytological oxidative stress. A cellular study showed that Cd capable to accumulate in pancreas causing beta cell dysfunction and inhibits insulin secretion (El Muayed *et al.* 2012). Another study showed Cd decrease beta cell viability and induce beta cell death (Chang *et al.* 2013). Microscopic examination found both α-cells and β-cells are separated from each other in Cd exposure group (Edwards and Prozialeck 2009). The affected cell shape was irregular, poor cell body volume, and evidence of infiltration of the red blood cell in the area of Islets of Langerhans. These evidences showed massive disruption of pancreatic cell morphology and altered cell adhesion due to Cd exposure. In an animal study, Edward and Prozialeck also found a dose-dependent effect with the decrease of gene mRVA levels in pancreas of rats that exposure to Cd. Even after 12 weeks of exposure, Cd still present in pancreatic cells. The study further found direct toxicity towards pancreas by the increased percentage of HbA1c, as well as reduction of fasting serum insulin. Result from the Malmo Diet study showed blood Cd is associated with Haemoglobin A1c (HbA1c) but not with blood glucose level and serum insulin. Available data suggested that Cd is able to accumulate in red blood cells and increase HbA1c (Fagerberg *et al.* 2015). A study in Pakistan clearly demonstrated high Cd concentrations in scalp hair of diabetic patient (Afridi *et al.* 2013). These epidemiological and cellular studies indicate Cd may exacerbate or play a responsibility 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 other study (Shapiro *et al.* 2015; Yang *et al.* 2015).

Conclusion

Until now, there is no research investigating the relationship between Cd exposure and DM occurrence in Malaysia. Additional epidemiological and cellular studies are needed to rule out the effects of such confounding variables on the possible link between Malaysian diet, Cd exposure and diabetes mellitus occurrence. Exposure towards Cd may vary dependent on geography and sociocultural factor. Most of the route of exposure is through oral via Cd-contaminated foods. The long half life of Cd in various storage and target organ would potentially affect human health. There are strong associations from many studies between Cd and diabetes mellitus. But further epidemiological, cellular and toxicological studies, particularly in Malaysia are granted to confirm this association to ensure the protection of people from devastating Cd health effects such as diabetes mellitus.

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