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Original Article

Baseline Nickel Level in Saliva and Urine Among Healthy Malay Population

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ABSTRACT

Objectives: *Nickel is one of the common trace metal element used in industries. It has been documented that even in small quantities, prolonged exposure to nickel is cytotoxic, genotoxic and carcinogenic. Nickel biomonitoring has been done by various countries to monitor nickel level. However, there is little information on established baseline nickel level in our population which leads to the difficulty for comparison during nickel exposure. This study aims to determine the baseline nickel level in saliva and urine samples for the healthy Malay population.* **Materials and Methods:** *Fourteen healthy Malay subjects were recruited in this study. Saliva and urine samples were collected and analysed using Inductively Coupled Plasma Optical Mass Spectrometry (ICP-MS) to measure the nickel level. Statistical analysis was performed using IBM SPSS Version 27.* **Results:** *Results showed that the nickel level in urine was higher compared to saliva. The baseline nickel level exhibited in saliva was 4.80 ppb (95% CI: 2.23, 7.38) and in urine was 5.88 ppb (95% CI: 3.49, 8.27).* **Conclusion:** *To our knowledge, this is the first study to report the baseline nickel level in saliva and urine among the Malay population.*

Keywords: *baseline nickel level, Malay population, saliva, urine.*

INTRODUCTION

Nickel is the twenty-fourth most abundant metal element found in the earth's crust, and extensively distributed in the environment, air, water, and soil. Trace elements such as nickel are essential components in the biological structures of cells and have been reported to play important roles in human metabolic and physiological processes (Gumienna-Kontecka, et al., 2017). Nickel is one the common trace metal element used in manufacturing industries such as the production of coins, jewellery, nickel-cadmium batteries, and as a catalyst in food and chemical industries (Patra et. al., 2019). Nickel in metal alloys was used in dentistry as well due to their exceptional mechanical properties (Givan et al., 2014; Proffit et al., 2007). Long-term exposure to nickel, even in small amounts, has been shown to be cytotoxic, genotoxic, and carcinogenic. This has led to numerous research from different countries to determine the trace element levels in different biological samples (Moghadam et al., 2019; Guo et al., 2014; Mudjari et al., 2019; Dwivedi et al., 2015). Nevertheless, the nickel level can vary significantly within and between populations and geographical regions, depending on dietary habits, genetic variation, lifestyle and occupational environment. Two studies carried out in France used whole blood to analyse baseline nickel level using ICP-MS technique but reported different results (Nisse et al., 2017; Goulle et al., 2005). Moreover, with similar analytical technique and sample used, the documented baseline nickel level in saliva were heterogenous (Amini et al., 2012; Butt et al., 2020). Other studies which used blood serum to analyse the baseline nickel level conducted their experiment using different method and reported different values (Mohammed et al., 2020; Satija et al., 2014).

Furthermore, published reports indicated that even with the same analytical technique used, a standardised level of nickel baseline has not been confirmed. Most other studies used Inductively Coupled Plasma Mass Spectrometry (ICP-MS) due to its lowest detection limit and highly sensitive analytical technique for the determination of trace elements of clinical interest such as nickel from biological samples (Nisse et al., 2017; Mohammed et al., 2020; Komarova et al., 2021). Different types of biological samples were used in the past such as blood and hair. However, these types of samples are invasive, complex sample preparation and technique sensitive (Komarova et al., 2021; Imani et al., 2019). In this study, the use of saliva and urine have several advantages such as non-invasive collection, less discomfort, straightforward sample collection and easy to store and transport. In addition, salivary and urinary mechanisms play an important role in excreting nickel from the body and can reflect the baseline nickel level in human (Danial et al., 2019; Holm et al., 2016).

The baseline nickel level reported varies between previous studies. These contributes to the wide variability of baseline nickel level in human (Komarova et al., 2021; Khaneh et al., 2017). As a result, there is little information on established baseline level of nickel in our population and this leads to the difficulty for comparison during nickel exposure. This study aims to determine the baseline nickel level in saliva and urine samples among the healthy Malay population.

MATERIALS AND METHODS

This prospective study was conducted at the Faculty of Dentistry, Universiti Teknologi MARA (UiTM) Sg. Buloh Campus. Ethical approval was granted from UiTM Research Ethics Committee on 28th March 2019 (reference number: 600-IRMI (5/1/6)). Fourteen voluntary subjects were conveniently selected based on stringent inclusion and exclusion criteria. Subjects must be in a permanent dentition and have no history of orthodontic treatment. Subjects who have any systemic illness, under long-term drug therapy, presence of amalgam restorations or oral and body prostheses, presence of tongue or lip piercing, smoker or had betel nut chewing habit, were excluded. All sample collection were done in the morning.

Sample Collection

All subjects were instructed to rinse their mouth thoroughly before saliva collection and to minimise their orofacial movements. Five ml of unstimulated saliva was collected using passive drooling method into a 50 ml sterile plastic centrifuge tube. For urine collection, subjects were provided with a 50 ml sample collection bottle and were asked to collect urine after discarding the first flush. Instructions were given not to contaminate the collection bottle by wiping or rinsing the internal surface of the bottles. Each sample taken was stored immediately at -20C freezer until further analysis.

Sample Analysis

Inductively Coupled Plasma Mass Spectrometry (ICP-MS) (ELAN 9000 Perkin Elmer) was used to determine the nickel level. For each sample, the test was repeated three times and the mean reading was taken as the final value of nickel level. All results were detected by computer software and presented as mean nickel level.

Statistical Analysis

Results obtained were subjected to statistical analysis using the Statistical Software for Social Science (IBM SPSS Statistics, Version 27). The level of statistical significance was set at $p < 0.05$. Descriptive analysis was used to analyse the socio-demographic data such as age and gender.

RESULTS

The results of this study showed that the mean (SD) subjects' age was 31.57 (3.74) years old and 71% (n=10) were female. It can be seen from the data in Table 1, the proportion of female subjects were more than two times higher than male. However, there was no difference of nickel level observed between genders ($p > 0.05$).

As shown in Table 2, the mean nickel level exhibited in saliva was 4.80 ppb (95% CI: 2.23, 7.38) and in urine was 5.88 ppb (95% CI: 3.49, 8.27). The results also showed that the nickel level in urine was higher compared to saliva.

Table 1: Frequency analysis based on gender

	Frequency	Percent
Male	4	28.9
Female	10	71.1
Total	14	100.0

Table 2: Baseline nickel level in saliva and urine among Malay population

	Baseline nickel level (95% CI)
Saliva	4.80 ppb (2.23, 7.38)
Urine	5.88 ppb (3.49, 8.27)

DISCUSSION

The International Agency for Research on Cancer (IARC) has identified nickel and its compounds as human carcinogens, and the toxicity depends on the physico-chemical characteristics, the dosage, route of exposure and solubility of the nickel compounds in humans (Genchi et al., 2020; IARC, 2018). It is well documented that nickel induced change in tumour suppressor p53 gene, cell apoptosis and cancer risks. Other than that, nickel can cause a variety of health effects, such as contact dermatitis, cardiovascular disease, asthma, lung fibrosis, and respiratory tract cancer.

The baseline level of nickel in a population is essential for nutritional and clinical monitoring of potential exposures. Due to increased exposure to trace elements including nickel element, there have been several studies to establish reference ranges in France, Australia, Pakistan and Iran (Nisse et al., 2017; Amini et al., 2012; Butt et al., 2020; Komarova et al., 2021).

Previous studies strongly emphasised that the evaluation the baseline nickel level should be conducted in different populations, as the levels may vary significantly between geographical regions, depending on dietary habits, genetic variation, lifestyle and occupational environment. Thus, these factors support the need to evaluate the nickel level among the Malaysian population as reported in this study (Komarova et al., 2021; Khaneh et al., 2017).

To the best of our knowledge, this study represents the first report to analyse the reference value of salivary and urinary nickel levels among the Malay population. In this present study, we observed that the mean salivary and urinary nickel level was 4.80 ppb (95% CI: 2.23, 7.38) and 5.88 ppb (95% CI: 3.49, 8.27), respectively. There has been a study involving Malaysian population using blood serum and the reported mean nickel level was 5.12 ppb(13). These reported baseline nickel values for Malaysian population are similar but consideration must be taken that different biological samples were used. We believe our baseline nickel level in saliva and urine can be utilised in future research involving nickel element among Malay population.

In the present study, saliva and urine were collected as biological samples to evaluate the nickel level. Human saliva composition was proven by numerous past studies that it can provide information to many clinical, experimental and diagnostic protocols (Michalke et al., 2014; Pfaffe et al., 2011) while urine has the ability to reflect systemic nickel levels in human due to its metabolic route is through the kidneys (Guo et al., 2014, Holm et al., 2016). Both saliva and urine are considered more tolerable to subjects because they are non-invasive techniques, accessible, convenient, and require simpler handling and sample preparation (Jayachandran et al., 2020; Pathiyil et al., 2019; Wang et al., 2015).

Khlifi et al. reported that there was no significant difference in blood nickel level for men and women (Khlifi et al., 2014). This is in line with our results where we found that there was no difference of nickel level observed between genders. However, our subjects consisted of 71% female. In contrast, Gil et al. have found higher blood and saliva nickel levels in women (Komarova et al., 2011).

It is noteworthy to mention that different methods of sample preparation and analytical technique used will provide heterogenous result. In this study, ICP-MS was used to analyse the level of nickel in the saliva and urine samples, which was similar to recent studies (Moghadam et al., 2019; Dwivedi et al., 2015; Nayak et al., 2015). ICP-MS is a robust and widely used technique, have low detection limit and highly sensitive for nickel analysis (Enamorado et al., 2013).

The baseline nickel level in saliva and urine for Malay population found in this study was 4.80 ppb (95% CI: 2.23, 7.38) and 5.88 ppb (95% CI: 3.49, 8.27), respectively. A future population-based study with larger sample size using different biological samples is suggested.

CONCLUSION

This is the first study determining the nickel level in saliva and urine among Malay population. Results showed that the baseline level of nickel in saliva was 4.80 ppb (95% CI: 2.23, 7.38) and in urine was 5.88 ppb (95% CI: 3.49, 8.27). We believe our study can be applied for the determination of nickel level in different study as for example long term use of orthodontic appliance. It could be useful in future research that requires a baseline nickel level. Additional studies are required to establish the nickel baseline level for the Malaysian population with different biological samples.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest related to the contents of this article.

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