Induction of an Autoimmune Thyroid Disease After Subcutaneous or Oral Sodium Silicate Challenge

Oral veya Subkutan Sodyum Silikat Yüklemesi Sonrası Otoimmün Tiroid Hastalığının İndüksiyonu

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Abstract

Thyroid gland is a target organ for the hazards of some drugs and toxins. The objective of this experimental study is to demonstrate whether the subcutaneous or oral sodium silicate will induce autoimmune thyroid disease. In this study, twelve Brown Norway rats were selected from my previous study (Almogairen et al, Lupus 2009 April). At 14th week post sodium silicate or normal saline exposure, the rats were sacrificed and then thyroidectomized. Histopathological studies were done in autoantibody-positive silicate group of six rats and were compared with the equal number of rats in autoantibody-negative control group. Thyroid gland in the sodium silicate group showed epithelial follicular proliferation in 5/6 (83.33%) compared with 2/6 (33.33%) of the corresponding control saline group, p=0.12, but the absolute difference in the percentage between the two groups was 50%; thyroid gland in the subcutaneous sodium silicate sub-group showed epithelial follicular proliferation in a relatively significant number (p=0.05). When correlating the above results with Serum ANA response of the same rats, it might be concluded that sodium silicate may play a role in inducing autoimmune thyroid disease in an immunosensitive rats. *Turk Jem 2009; 13: 67-70*

Key words: Autoimmune, ANA, thyroid, silicate

Özet

Tiroid bezi bazı ilaç ve toksinler için hedef organdır. Bu deneysel çalışmanın amacı subkutan veya oral sodyum silikatın otoimmün tiroid hastalığını başlatıp başlatmayacağını araştırmaktır. Bu çalışma için, daha önceki çalışmamdan (Almogaıren et al., Lupus 2009 Nisan) 12 Norveç sıçanı seçildi. Sodyum silikat verilen ve normal sodyum klorür verilen sıçanlar 14 üncü haftada öldürüldü ve tiroidektomi yapıldı. Otoantikor pozitif olan silikat verilmiş gruptaki altı sıçan üzerinde histopatolojik incelemeler yapıldı ve otoantikor negatif olan kontrol grubundaki aynı sayıdaki sıçanlarla karşılaştırıldı. Sodyum silikat grubundaki sıçanların 5/6 sının tiroid bezinde (%83,33) epitelyal follikuler proliferasyon izlenirken bu oran kontrol sodyum klorür grubunda 2/6 (%33,33) idi (p=0,12). Ancak iki grup arasındaki kesin fark, oran olarak %50 idi; subkutan sodyum silikat alt grubunda, tiroid bezinde epitelyal follikuler proliferasyon görülen sıçanların sayısı diğerlerine göre oldukça fazla idi (p=0,05). Yukarıdaki sonuçlar, aynı sıçanların serum antinükleer antikor (ANA) cevabı ile ilişkilendirildiğinde, sodyum silikatın immünosensitif sıçanlarda otoimmün tiroid hastalığının indüklenmesinde önemli rol oynayabileceği sonucuna varılabilir. *Türk Jem 2009; 13: 67-70*

Anahtar kelimeler: Otoimmün, ANA, tiroid, silikat

Introduction

Silica exposure might be associated with autoimmune diseases such as scleroderma, systemic lupus erythematosus, and rheumatoid arthritis (1-3). Occupations having the potential for silica exposures include mining, quarrying, tunneling, glass manufacture, ceramics, pottery production, cement and concrete production (4-5). There are implants made of silicon for medical purposes such as cosmetic breast implants, cardiac valve replacement and joint implants (6-8). Thyroid gland is one of the targets to the hazards of toxins and drugs. These include amiodarone, lithium, cyclosporine, interleukin-2, interferon-alpha and propylthiouracil (PTU) (9-16).

The main finding of PTU-induced hypothyroidism in rats was attenuation of c-cells activity with hypoactivity of follicular cells, confirmed by histologic and ultrastructural studies (12). Only five papers describe the pathological findings in amiodarone-induced hyper-

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thyroidism and none in amiodarone-induced hypothyroidism (10). The aim of the present study is to investigate whether sodium silicate will induce autoimmune thyroid disease in immunosensitive rats. This study is an extension of a previous study (Almogairen et al, Lupus 2009 April) 17,but examines the correlation between the autoimmune response and the histopathological changes in the thyroid gland.

Materials and Methods

Brown Norway rats (BN) (average weight of 157 g) were purchased from Charles Rivers Laboratories, Wilmington, U.S.A. They were kept in polycarbonate metrolon plastic cages covered with stainless steel cover in the animal house in the College of Medicine, King Saud University, Riyadh, Saudi Arabia. They were maintained under 12-hr dark: 12-hr light cycles and were kept under observation for three weeks. No evidence of sickness was observed. All rats were 8-11 weeks old at the onset of the experiment. There were a total number of twelve rats divided into two main groups: silicate and control normal saline groups. There were four sub-groups, the first and the second sub-groups (six rats) were called subcutaneous silicate sub-group (three rats) and oral silicate sub-group (three rats). The third and the fourth sub-groups (six rats) were called subcutaneous normal saline control sub-group (three rats) and oral normal saline control sub-group (three rats).
All the above groups were selected for histological studies of the thyroid gland from my previous study, where the first and the second silicate sub-groups were autoantibody-positive for serum ANA, anti-dsDNA, anti-Smith, anti-SSA and anti-SSB. On the other hand, the third and the fourth control normal saline sub-groups were overall autoantibody-negative. The above selected subgroups after fourteen weeks of exposure to sodium silicate or normal saline were sacrificed and then thyroidectomized. The tissues taken from them were bisected and fixed in 10% buffered formalin for 24 hours. The tissues were then processed in the Tissue-Tek vacuum infiltration processor and stained using hematoxylin and eosin stain. The slides were examined blindly by histopathologist using light microscope.

Statistical Analysis

Statistical differences between silicate and the corresponding control groups were calculated using the Fisher's exact test.

Results

The maximum serum antibody titers in the selected rats from my previous study are shown in Table 1.
The histopathological results are shown in Table 2. The changes in the thyroid gland were considered as negative if all of the parameters shown in Table 2 were negative, otherwise, positive. The positive changes in the thyroid gland, depicted in Figure 1, were seen in 3/3 (p=0.05) of subcutaneous sodium silicate sub-group, on the other hand, p value was 0.8 in the oral sodium silicate sub-group. When comparing the whole silicate group, including the subcutaneous and the oral sub-groups (total number is 6), with the control normal saline group, including the subcutaneous and the oral subgroups (total number is 6), positive changes in the thyroid gland were seen in 5/6 (83.33%) of the silicate group. In contrast, the positive changes in the thyroid were observed in 2/6 (33.33%) of the control normal saline group (p=0.12). Figure 2 shows the normal histopathological features of the control group.

Discussion

Environmental crystalline silica exposure has been associated with formation of autoantibodies and development of systemic autoimmune diseases (1-3,18-21).
Occasionally, exposure to some drugs or toxins is associated with thyroid gland diseases.9-16 Experimental autoimmune thyroiditis is an organ-specific autoimmune disease that can be induced in genetically susceptible strains of mice by injection of thyroglobulin or IL2 (22).
In my previous study, only in the subcutaneous silicate sub-group there was an overall increase in the number of rats with positive titers of all autoantibodies tested post exposure to sodium silicate with significant p value ($p<0.05$) (17).
In the present study, the histopathological examination of the thyroid glands showed an epithelial follicular proliferation in all rats of the subcutaneous silicate sub-group, reaching a significant level of p value=0.05. Due to the constricted budget of the present study, the number of subjects in the sub-groups (oral or subcutaneous silicate groups) was limited to three. Therefore, we tried to augment

Table 1. Maximum serum antibody titres of the rast in which histopathology was performed

RATS	ANA (≤1/10) significant	Anti-dsDNA (≥0.08) significant	Anti-Smith (≥0.06) significant	Anti-SSA (≥0.12) significant	Anti-SSB (≥0.05) significant
Silicate SC1	1/80	-ve	0.152	-ve	-ve
Silicate SC2	1/80	-ve	-ve	-ve	-ve
Silicate SC3	1/80	-ve	-ve	-ve	-ve
Silicate PO1	1/20	-ve	0.06	0.109	-ve
Silicate PO2	-ve	-ve	-ve	0.24	-ve
Silicate PO3	-ve	0.08	0.06	0.16	1.7
Control SC1	-ve	-ve	0.06	-ve	-ve
Control SC2	-ve	-ve	-ve	-ve	-ve
Control SC3	-ve	-ve	-ve	-ve	-ve
Control PO1	-ve	-ve	-ve	-ve	-ve
Control PO2	-ve	0.88	-ve	-ve	-ve
Control PO3	-ve	-ve	-ve	-ve	-ve

SC: Subcutaneous
PO: Per oral
-ve: Negative

the number of subjects by comparing the silicate group, including the subcutaneous and the oral sub-groups (total number is 6), with the control normal saline group, including the subcutaneous and the oral sub-groups (total number is 6). The absolute difference in the percentage between the two groups was equal to 50% (83.33%-33.33%), which is clinically useful, although, we did not achieve statistical significance (p=0.12).

The mechanism of these histopathological changes is probably due to disruption of one of the following physiological systems: the hypothalamic-pituitary-thyroid (HPT) axis, the calcium metabolism, and immunosuppression (23).

The significant serum autoimmune response, particularly with ANA, suggests that the autoimmunity probably has a contribution to the histopathological histological changes in the thyroid gland. There are a limited number of publications concerning the structure of thyroid gland following the exposure to some drugs and toxins (9,10,12-14, 22-23).

To my knowledge, this is the first study showing the correlation between the histological changes in the thyroid gland secondary to silicate exposure and the serum autoimmune response.

In conclusion, silica exposure is probably one of the risk factors inducing autoimmune thyroid disease in immunosensitive rats.

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Table 2. Histopathological features of silicate-tested&control groups

Thyroid of the following rast	Inflammation	Autoimmune thyroiditis	Granuloma	Epithelial follicular proliferation	Hurthle cell	Neoplastic change
Silicate SC1	-ve	-ve	-ve	+	-ve	-ve
Silicate SC2	-ve	-ve	-ve	+	-ve	-ve
Silicate SC3	-ve	-ve	-ve	+	-ve	-ve
Silicate PO1	-ve	-ve	-ve	+	-ve	-ve
Silicate PO2	-ve	-ve	-ve	+	-ve	-ve
Silicate PO3	-ve	-ve	-ve	-ve	-ve	-ve
Control SC1	-ve	-ve	-ve	-ve	-ve	-ve
Control SC2	-ve	-ve	-ve	-ve	-ve	-ve
Control SC3	-ve	-ve	-ve	-ve	-ve	-ve
Control PO1	-ve	-ve	-ve	-ve	-ve	-ve
Control PO2	-ve	-ve	-ve	+	-ve	-ve
Control PO3	-ve	-ve	-ve	+	-ve	-ve

-ve = 0 = negative
+ = 1 = mild
++= 2 = moderate
+++ = 3 = severe
SC: subcutaneous
PO: per oral

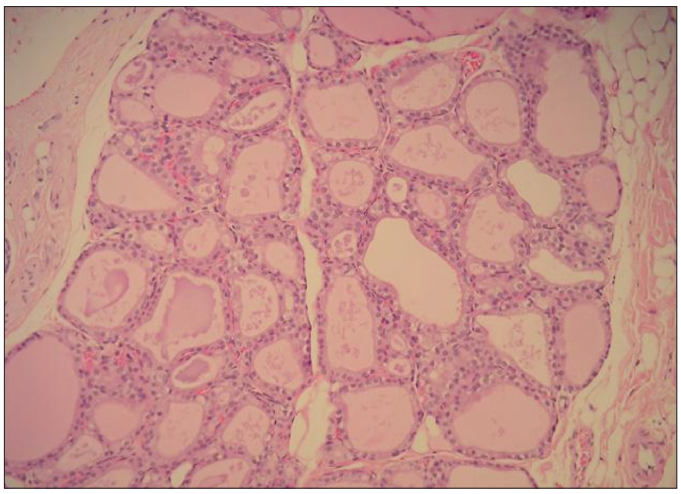

Figure 1. Rat thyroid, hematoxylin and eosin stain (x200 magnification). Sections show histology of thyroid gland. There is moderate proliferation of thyroid follicles. These are actively secreting small thyroid follicles with scanty colloid. The cuboidal cells lining the follicle are relatively tall, reflecting active hormone synthesis

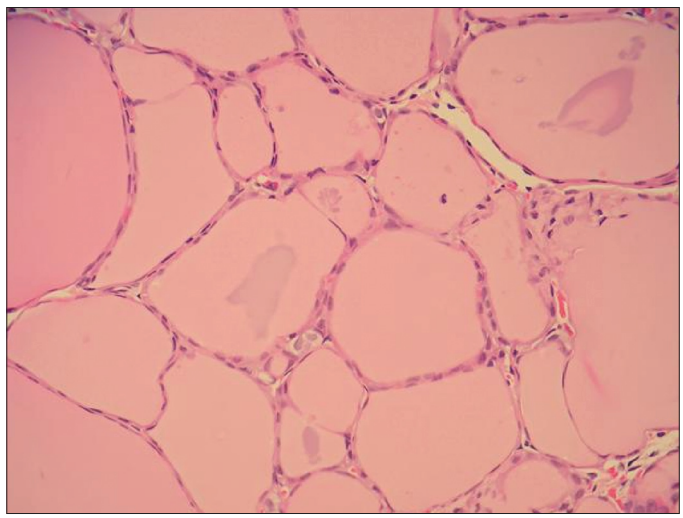

Figure 2. Rat thyroid, hematoxylin and eosin stain (x200 magnification). Sections show histology of thyroid gland from the control rats. The thyroid follicles are lined by simple flattened to cuboidal epithelium. These thyroid follicles are distended and filled with pink colored colloid

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