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Moderate-dose simvastatin therapy potentiates the effect of vitamin D on thyroid autoimmunity in levothyroxine-treated women with Hashimoto's thyroiditis and vitamin D insufficiency

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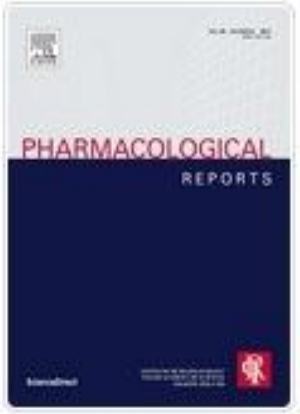

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Subject	Rank/Out of	Quartile	Percentile
Pharmacology	107/302	Q2	64%

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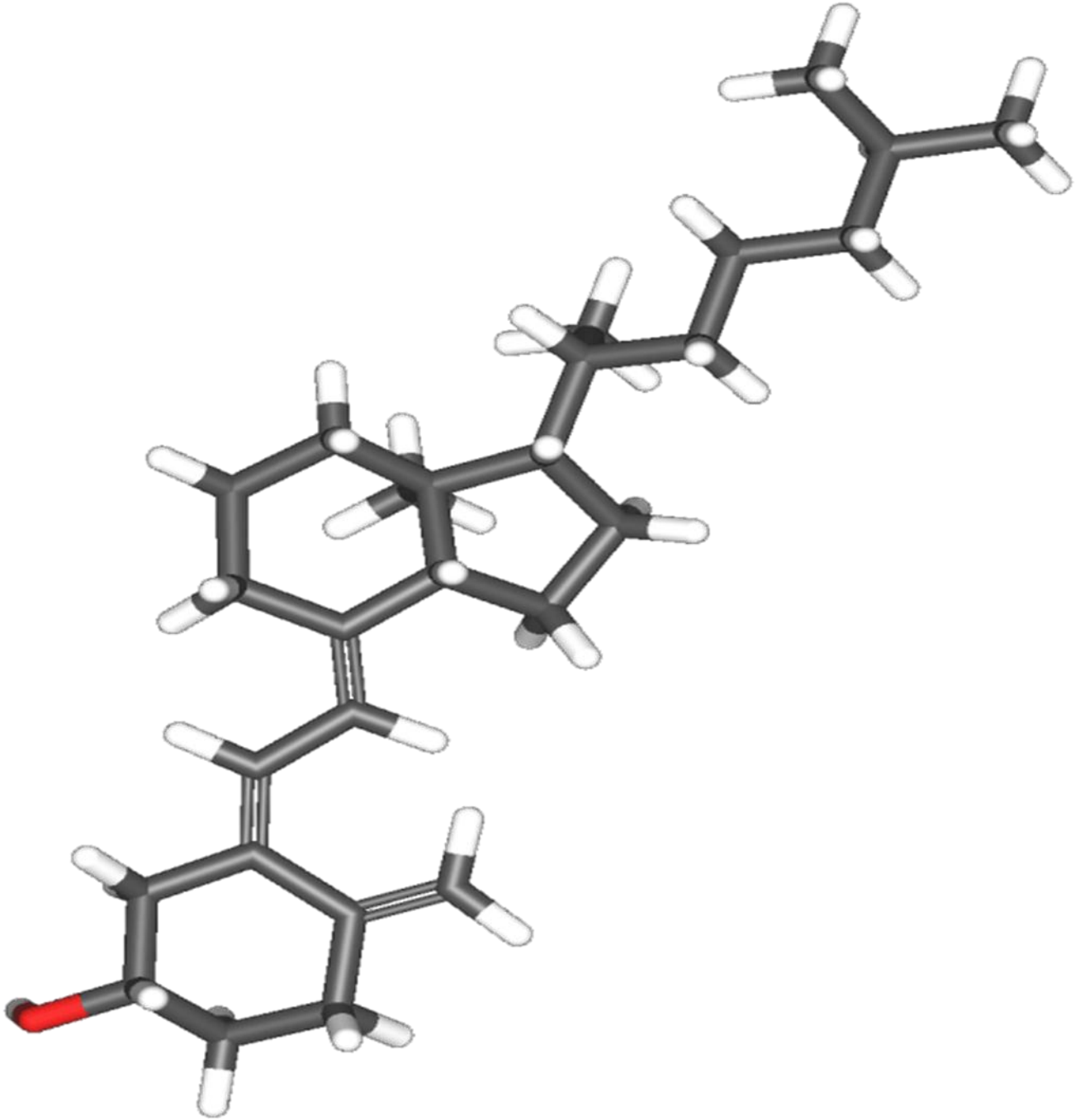
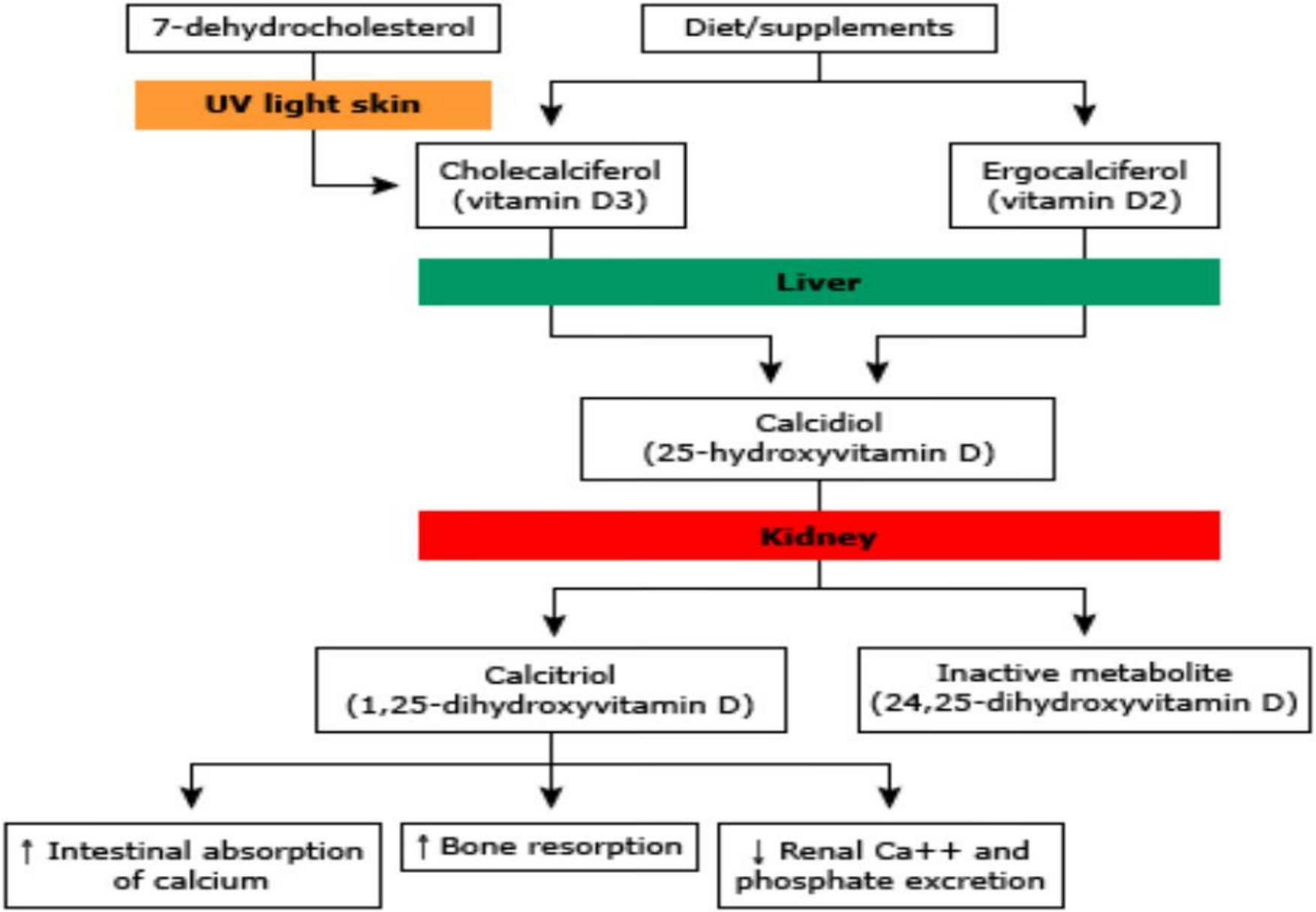


Pathways of vitamin D synthesis



Introduction

- The role of Vitamin D:

MS, RA, and DM(type I).

the relationship between Vit D and AITDs is still a controversial issue.

Many studies have already pointed out a relation between low concentration of Vit D and AITDs

Another investigation

Effect of Vitamin D deficiency treatment on thyroid function and autoimmunity markers in Hashimoto's thyroiditis: A double-blind randomized placebo-controlled clinical trial

- The effect of Vit D treatment on TPO-Ab and TSH in Vit D deficient hypothyroid or euthyroid adult patients with positive TPO-Ab:
- Vit D did not have a significant effect on thyroid function and autoimmunity.

Vitamin D Treatment in Patients with Hashimoto's Thyroiditis may Decrease the Development of Hypothyroidism.

- Vita D deficiency is frequent in Hashimoto's thyroiditis.
- Vit D measurement and replacement may be critical in these patients.

The Role of Vitamin D in Thyroid Diseases (R.A)

- Beneficial role of vit D in the management of thyroid disease.
- The preventive and therapeutic potential of vit D or its analog in thyroid diseases remains debated.

Introduction

- Hashimoto's thyroiditis, the commonest thyroid disorder in iodine-sufficient areas
- characterized by thyroid homing of autoreactive T-helpers, cytotoxic T-lymphocytes and natural killer cells.

Introduction

- Is associated with antibody-mediated cytotoxicity and apoptosis.
- Progressive loss of follicular cells.
- Replacement of the thyroid tissue by lymphoid lymphocytic infiltrate and fibrotic reaction.

Introduction

- Autoimmune thyroiditis and low vit D status and it′s association is independent of sex, age and body mass index.
- The severity of vit D deficiency correlates with Anti TPO titers, gland volume, as well as with the duration of Hashimoto’s thyroiditis.

Introduction

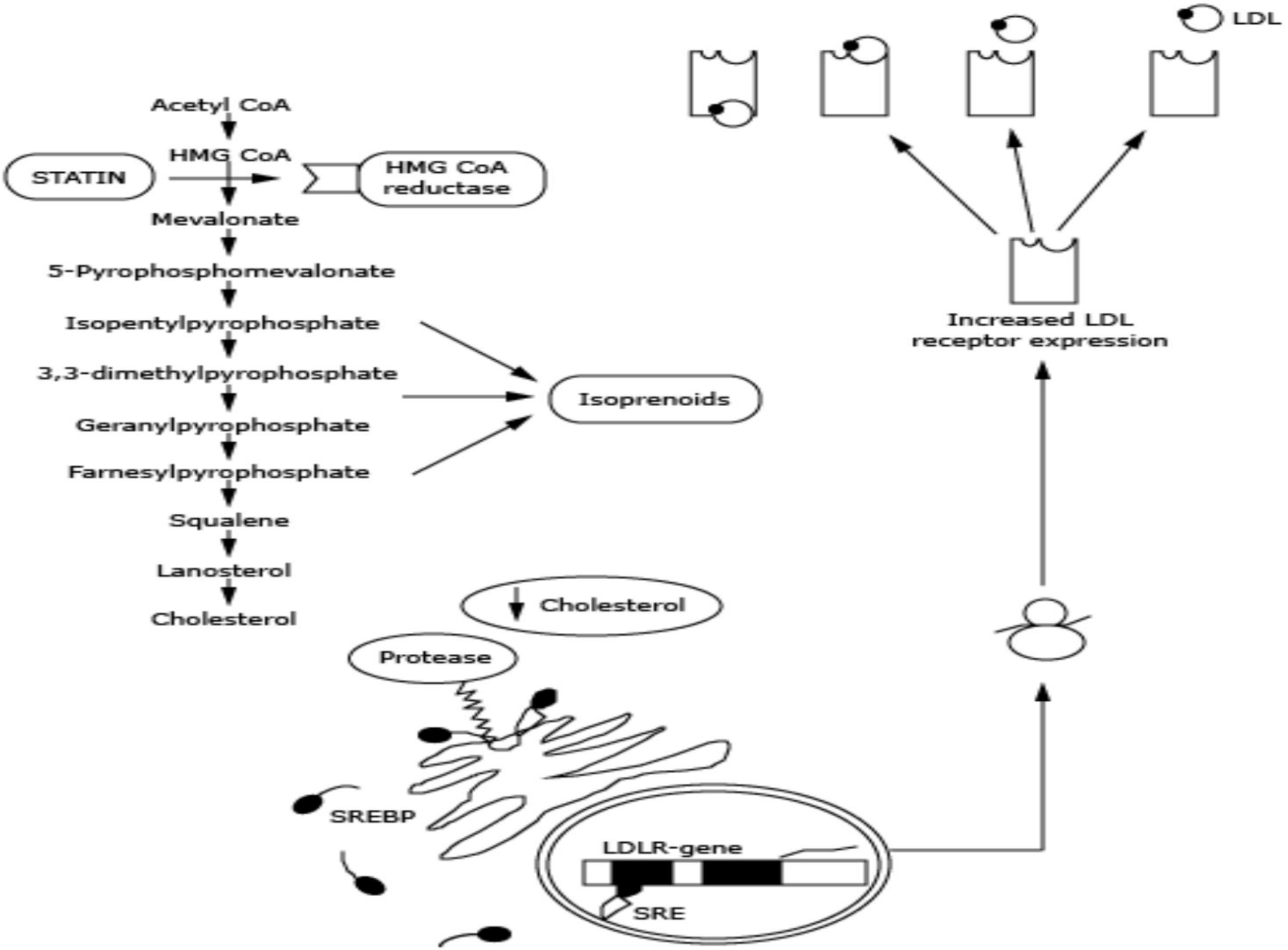
- Recent meta-analysis shows:
- Lower levels of ٢٥-OH vit D, subjects with Hashimoto's thyroiditis

Introduction

- Vit D supplementation and Anti TPO titers and this effect in women postpartum thyroiditis with vit D deficiency and vit D insufficiency.
- vit D reduces titers of Anti TPO and to a lesser extent also thyroglobulin antibodies in women with normal vit D status.

Introduction

- Generally accepted that extra-lipid (pleiotropic) effects of HMG-CoA RI, or statins, include anti-inflammatory and immune modulatory effects.


LDL
Acetyl CoA
HMG CoA
STATIN
HMG CoA reductase
Mevalonate
5-Pyrophosphomevalonate
Isopentylpyrophosphate
3,3-dimethylpyrophosphate
Geranylpyrophosphate
Farnesylpyrophosphate
Isoprenoids
Squalene
Lanosterol
Cholesterol
Increased LDL receptor expression
Cholesterol
Protease
SREBP
LDLR-gene
SRE

Introduction(HMG-COA RI effect)

- Shift cytokine profile from Th١/Th١٧ to Th٢ type cytokines
- Inhibit proliferation and activation of T lymphocytes
- Enhance apoptosis of T cells
- Decrease degranulation and cytotoxicity of natural killer-cells,
- Attenuate the interferon-γ effect.

Introduction

- Simvastatin and atorvastatin significantly reduce (HLA-DR) on thyrocytes with Hashimoto's thyroiditis,
- Decrease HLA-DR expression in thyroid cells with autoimmune thyroiditis and healthy control.

Introduction

- Statins reduce lymphocytes and improve thyroid function tests
- Intensive, but not less aggressive, statin therapy reduced thyroid autoimmunity in female patients with Hashimoto's thyroiditis.

Introduction

- The present study was aimed at assessing whether the effect of vit D on thyroid autoimmunity in women with Hashimoto's thyroiditis is affected by statin use.

Materials and methods

- The study included fifty-seven levothyroxine-treated euthyroid women with Hashimoto's thyroiditis and vit D insufficiency, aged ٢٥ - ٥٠ yr.
- Hashimoto's thyroiditis was diagnosed if the women had TPO-Ab >١٠٠ U/ml & reduced echogenicity of the thyroid parenchyma on US.

Materials and methods

- Vit D insufficiency:
- Serum ٢٥-OH-vit.D = ٢٠ - ٣٠ ng/mL.
- Women with TSH = ٠.٤٥ - ٤.٥ mU/l and free thyroid hormone within the reference range receiving levothyroxine treatment (٧٥–١٢٥ μg daily) for at least six months.
- Moreover, ٢/٣ of participants were required to have isolated hypercholesterolemia defined as LDL >١٣٠ mg/dL.

Materials and methods

- The exclusion criteria:
- Acute and chronic inflammatory processes, other autoimmune disorders
- Pituitary or parathyroid gland disorders
- Symptomatic CHF, CAD, moderate or severe Htn (E.S.C /E.S.Htn grade ٢ or ٣)
- DM, impaired renal or liver function
- Pregnancy or breastfeeding,

Materials and methods

- The exclusion criteria:
- Treatment with Se or with any lipid-lowering agents within ۶ months before the beginning of the study
- Concomitant treatment with Ca supplements, concomitant treatment with drugs affecting plasma lipid levels or Ca/phosphate homeostasis,
- Concomitant treatment with drugs known to interact with statins or vit. D, and poor patient compliance.

Materials and methods

- Seasonal fluctuations in vit. D status:
- Half of patients (n = ٣٠) were recruited in Jan. and Feb. the remaining ones (n = ٢٧) between July and August.

Materials and methods

- Ethics:
- The study protocol was approved by the local ethics committee and each woman gave a written informed consent before participation in the study. The experiments comply with the current law of Poland.

Study design

- Patient grouping:
- Group A (n = ١٨) : women not wishing to receive vit.D supplementation, in whom LDL were elevated.
- Group B (n = ١٩): had elevated LDL levels and accepted treatment with vit. D preparations.
- Group C (n = ٢٠): women with normal LDL who accepted treatment with vit. D.

Study design

- Groups A and B treated with simvastatin (٤٠ mg daily) in the evening.
- Women groups B and C received oral vit. D (٢٠٠٠ IU daily).
- Drugs administered for six months.
- All women continued levothyroxine treatment without any changes in dosage during the study.
- Compliance assessment was performed during each visit and was regarded as satisfactory if the number of tablets returned ranged from ٠% to ١٠%.

Laboratory assays

- Venous samples for lab. were obtained at ٨:٠٠ a.m. with ١٢-h fasting in the first day of the study and six months later.
- Plasma levels of total chol., LDL, HDL and TG were assayed by routine laboratory techniques.

Laboratory assays

- LDL were measured directly.
- TSH , FT۴ and FT۳, as well as serum titers of Anti TPO and anti Tg were determined by direct chemiluminescence using acridinium ester technology.
- ۲۵-OH Vit D were determined by enzyme immunoassay.
- All measurements were performed in duplicate and final results were averaged.

Statistical Analysis

- Because of skewed distributions, hormone levels and Ab titers we log-transformed to achieve a normal distribution before statistical analyses.
- The differences between baseline and post-treatment values within the same group were compared with the Student's paired t-test.

Statistical Analysis

- Using analysis of covariance followed by Bonferroni's multiple comparison test
- Categorical variables were analyzed by χ^2 test.
- Pearson's r-tests.
- P values < ٠.٠٥ were considered statistically significant.
- Potential confounders:

age, smoking, BMI, season during which samples were collected.

Results

- All groups were comparable with respect to age, smoking, BMI, medical history, TSH, FT۴ and FT۳.
- Total and LDL cholesterol were higher in groups A and B than in group C .
- All patients completed the study and were included in the final analyses.

Results

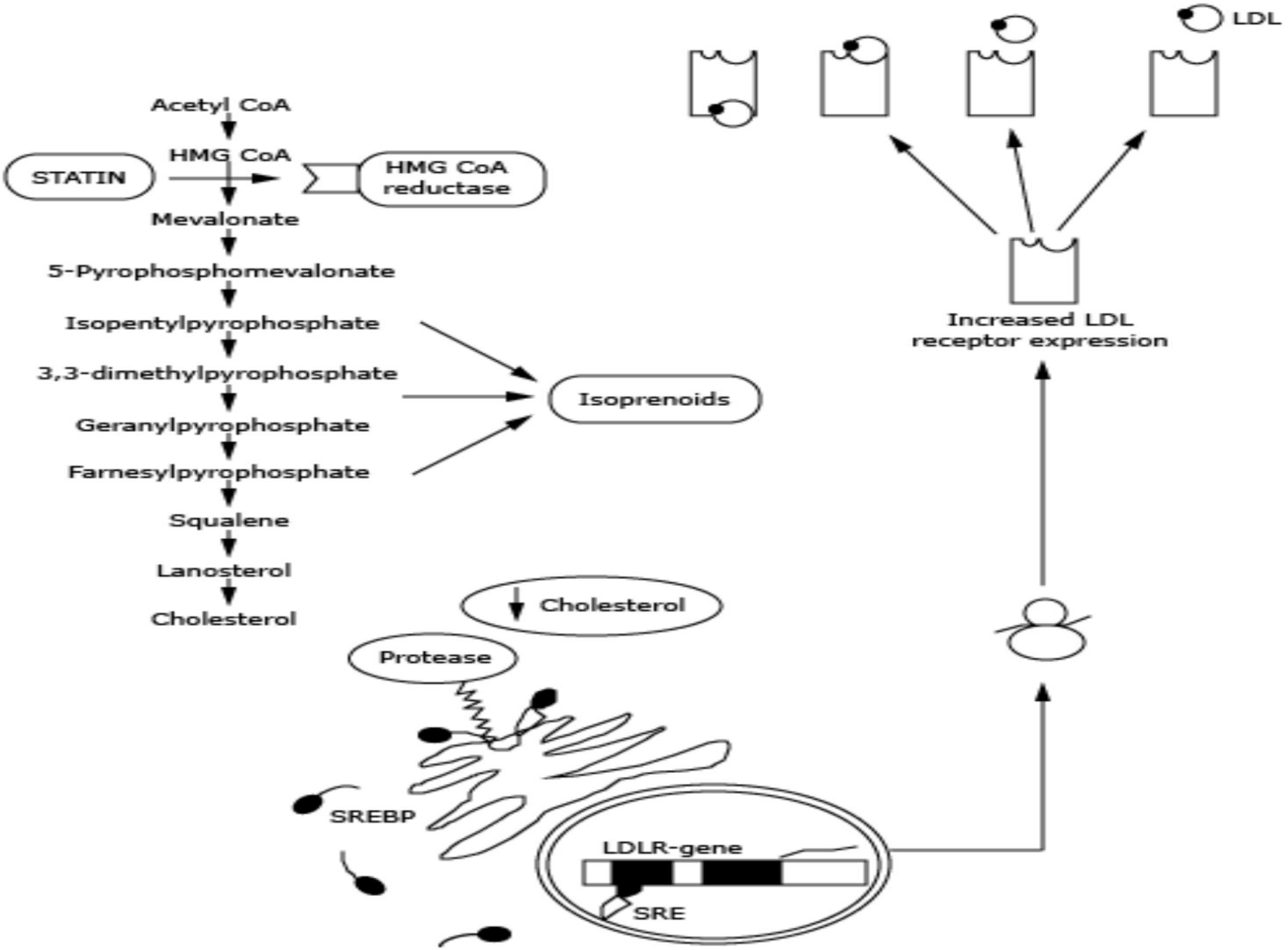
- As expected, simvastatin reduced plasma levels of total and LDL cholesterol in women with hypercholesterolemia, with no difference in the strength of action between the groups A and B .
- The drug did not affect circulating levels of HDL, TG, TSH, FT٤, FT٣, antibody titers and ٢٥-OH Vit D levels. Vit. D, administered alone or in combination with a statin, increased ٢٥-OH Vit D levels.

Results

- In group C: vit D decreased titers of TPO & Tg antibodies.
- In group B: simvastatin-vit D combination therapy reduced TPO and Tg antibodies and this effect was stronger than the effect of simvastatin and vit D administered alone.
- The effect of treatment on TPO and |Tg antibodies was stronger in group B than group C.
- No changes in TSH and free thyroid hormones were observed in any treatment group .

Discussion

- Moderate doses of simvastatin may potentiate thyroid antibody-lowering effect of vit D.
- This effect cannot be explained by simple additive effects of both **agents**.


LDL
Acetyl CoA
HMG CoA
STATIN
HMG CoA reductase
Mevalonate
5-Pyrophosphomevalonate
Isopentylpyrophosphate
3,3-dimethylpyrophosphate
Geranylpyrophosphate
Farnesylpyrophosphate
Isoprenoids
Squalene
Lanosterol
Cholesterol
Increased LDL receptor expression
Cholesterol
Protease
SREBP
LDLR-gene
SRE

Discussion

- In our previous study, simvastatin (٢٠ or ٤٠ mg daily) for a similar period of time produced a neutral effect on TPO and Tg antibodies .
- The results suggest that statin/vit D combination therapy may be an interesting treatment option for women with Hashimoto’s thyroiditis.

Discussion

- This combination therapy may bring benefits particularly to subjects with concomitant presence of CAD and/or to patients with elevated levels of LDL, who according to contemporary recommendations require statin therapy.

Discussion

- The present findings are in agreement with our previous results indicating that the strength of pleiotropic effects of atorvastatin depends on vit D status and is more pronounced in vit D-naïve patients with vit D insufficiency than vitamin D-treated men with vit D deficiency/insufficiency and healthy subjects .

Discussion

- It seems to be interesting in light of the fact that hypothyroidism develops particularly frequently and rapidly in subjects with the highest titers of thyroid antibodies and therefore these patients may be another important group of candidates for statin/vit D combination therapy.

Discussion

- Treatment-induced changes in titers of TPO antibodies were more pronounced than the changes in titers of Tg antibodies, which is in line with higher sensitivity of the former and at least equal specificity in the diagnosis of autoimmune thyroid disease .

Discussion

- Statins were found to inhibit the growth of thyroid epithelial cells and to stimulate thyrocyte apoptosis.
- Using these agents was associated with a reduced secretion of proinflammatory cytokines by activated human lymphocytes .

Discussion

- Vit D is made in the skin from ٧-dehydrocholesterol, being an immediate precursor of cholesterol .
- Consequently, low vit D status may be compensated by increased synthesis of non-sterol mevalonate derivatives, the effect opposite to that produced by HMG-CoA reductase inhibitors

Discussion

- Moreover, it cannot be fully ruled out that statins are either precursors of vit D receptors and/or are able to stimulate vit D receptors . However, a neutral effect of simvastatin on ٢٥-OH vit D levels in our study makes this explanation less likely.

Discussion

- Limitations:

The small sample

Despite the fact that antibody titers were similar in all study groups and did not correlate with total and LDL levels, while changes in TPO and Tg titers were lipid-independent, the impact of differences in plasma lipids on the obtained results cannot be totally excluded.

Discussion

- Due to obligatory salt iodization in our country , the question whether the effect of a statin and vit D is similar in iodine-deplete areas requires further research.
- Finally, it cannot be completely ruled out that the results of the study might have been partially affected by seasonal variation in ٢٥-OH Vit D levels .

Discussion

- Vit D, particularly administered together with a statin, reduced circulating titers of thyroid antibodies in vit D-deficient women with autoimmune thyroiditis.
- This effect correlated with the severity of thyroid inflammation and the strength of action on ٢٥-OH Vit D levels.

Discussion

- Simvastatin/vit D combination therapy may bring clinical benefits to some groups of women with Hashimoto's thyroiditis already receiving levothyroxine treatment.