Summary

Subclinical disease is an illness that stays below the surface of clinical detection , and has no recognizable clinical findings. Many diseases, including diabetes, hypothyroidism , hyperthyroidism and rheumatoid arthritis, can be subclinical before surfacing as clinical diseases.

Subclinical Hypothyroidism:

Subclinical Hypothyroidism (SCH) is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine. Subclinical hypothyroidism is most commonly caused (50-80% of cases) by chronic autoimmune thyroiditis, less frequently, inflammatory thyroiditis , patients who have previously undergone partial thyroidectomy and those treated with I^{131} , patients treated with external neck X-ray therapy, especially during infancy and adolescence, finally, SCH is diagnosed in 17.6% of L-thyroxine-treated hypothyroid patients due to insufficient L-thyroxine administration

Possible Consequences of Subclinical Hypothyroidism:

- Cardiac dysfunction or adverse cardiac end points (including atherosclerotic disease and cardiovascular mortality),
- Elevation in total and low-density lipoprotein (LDL) cholesterol,
- Systemic hypothyroid symptoms or neuropsychiatric symptoms,
- Progression to overt symptomatic hypothyroidism, patients with subclinical hypothyroidism have a high rate of progression to clinically overt hypothyroidism, 2.6% each year if thyroperoxidase (TPO) antibodies are absent and 4.3% if they are present. A TSH

level greater than 10 mIU/L predicts a higher rate of progression, and a level of less than 6 mIU/L predicts a lower likelihood of progression.

Asymptomatic patients with serum TSH levels between 4.5 and 10 μU per mL should have a repeat test every six to 12 months. patients with symptoms of hypothyroidism whose serum TSH concentration is between 4.5 and 10 μU per mL patients may try levothyroxine to see if symptoms improve. The panel recommends treatment with levothyroxine for patients with serum TSH levels greater than 10 μU per mL.

Subclinical Hyperthyroidism:

Subclinical Hyperthyroidism is defined as a serum TSH concentration below the statistically defined lower limit of the reference range when serum FT_4 and T_3 concentrations are within their reference ranges. Subclinical hyperthyroidism may be caused by exogenous or endogenous factors. The exogenous form of subclinical hyperthyroidism is usually related to TSH-suppressive therapy with L-thyroxine. TSH may be suppressed during hormone replacement therapy in about 20% of hypothyroid patients. The endogenous form is usually related to the same causes as overt thyrotoxicosis, namely Graves' disease, autonomously functioning thyroid adenoma, and multinodular goiter. The prevalence of exogenous and endogenous subclinical hyperthyroidism in the general population is between 0.7 and 12.4%. Subclinical hyperthyroidism is common during L-T_4 therapy, being present in about 10–30% of patients. **Features of Subclinical Hyperthyroidism** Include potential adverse effects on the cardiovascular system and the skeleton, and the presence or absence of symptoms or mood disturbance consistent with thyrotoxicosis.

The consensus panel's recommendations to observe and monitor patient's with partial TSH suppression (0.1–0.4 mU/liter), but to treat patients with complete TSH suppression (<0.1 mU/liter).

Accidentally Discovered Thyroid Nodule:

Incidentally discovered thyroid lesions have become increasingly common with the development and more frequent utilization of highly sensitive imaging modalities throughout the clinical practice of medicine. Determining the most appropriate management of these "incidentalomas" has presented a significant challenge to both endocrinologists and endocrine surgeons. Thyroid incidentalomas are defined as lesions revealed during imaging of the cervical region for indications other than thyroid disease. In most studies that used neck ultrasonography, thyroid nodules were detected in about one-third of the population.

Clinical Outcome: The major concern when faced with an incidentally detected thyroid nodule is the exclusion of thyroid cancer. Nevertheless, the incidence of thyroid cancer is relatively low compared with the extraordinarily high incidence of thyroid nodules, suggesting that most of these nodules are benign. The majority of cases of thyroid cancer depicted as thyroid incidentalomas are well-differentiated papillary carcinomas associated with a low cause-specific mortality.

The Ultrasound Phenotype: Ultrasonographic characteristics associated with malignancy are marked hypoechogeneity, irregular or microlobulated margins, microcalcifications, chaotic arrangement or intranodular vascular images and a rounded appearance. The specificities of the aforementioned features for detecting thyroid cancer vary greatly, from 41.4% to 95.0%, but their sensitivities are consistently very low.

However, the probability of malignancy increases significantly when two or more suspicious criteria coexist.

The Need for Fine-Needle Aspiration: The size of the depicted nodule is an important determinant of the need for further evaluation. Proceeding to fine-needle aspiration (FNA) cytology of lesions >1.0-1.5 cm is recommended, unless the ultrasound features are highly suggestive of benignity, such as isoechogenicity with a spongiform appearance. Patients who should undergo FNA testing are those that are either very young (<14 years) or old (>70 years), those with a history of malignancy, particularly if their treatment involved radiation of the neck, family history of medullary or papillary thyroid carcinoma or thyroid cancer syndrome, those with nodules >1.0-1.5 cm or suspicious nodule composition on ultrasonography, suspicious cervical lymphadenopathy.

Endocrine Assessment: The initial step of the endocrine assessment in patients with thyroid incidentalomas is the measurement of TSH levels. A normal result precludes further tests, whereas a low or high level of TSH should be further evaluated for the presence of hyperthyroidism, by measuring free T_3 or T_3 levels, or hypothyroidism, by measuring free T_4 or T_4 levels. Measurement of serum thyroid peroxidase (TPO) antibodies, which suggest autoimmune thyroiditis, is indicated in the presence of increased TSH levels.

Management: Further management of patients with thyroid incidentalomas depends largely on the results of FNA cytology. Benign nodules are managed conservatively with clinical and ultrasonography follow-up, whereas surgery is indicated in malignant and suspicious lesions. Cytology cannot discriminate between malignant and benign

follicular neoplasms, and most patients with this diagnosis will ultimately require surgery.

Subclinical Diabetes(pre-diabetes):

Subclinical Diabetes is form of diabetes mellitus that is clinically evident only under certain circumstances, such as pregnancy or extreme stress. The categories of impaired glucose tolerance and impaired fasting glucose have been officially termed prediabetes, because they are risk factors for future diabetes and for cardiovascular disease. Impaired fasting glucose is defined as glucose levels of 100 to 125 mg per dL in fasting patients. Impaired glucose tolerance is defined as two-hour glucose levels of 140 to 199 mg per dL on the 75-g oral glucose tolerance test. The natural history of both IFG and IGT is variable, with 25% progressing to diabetes, 50% remaining in their abnormal glycemic state, and 25% reverting to normal glucose tolerance over an observational period of 3–5 years. IFG and IGT frequently are associated with metabolic syndrome. There is now strong evidence that the onset of diabetes in people with IGT can be delayed or prevented by both behavioural and pharmacological interventions .

Subclinical Hyperparathyroidism:

Subclinical Hyperparathyroidism is when the blood parathyroid hormone (PTH) levels are higher than normal but the blood calcium level is normal in patients who do not have secondary hyperparathyroidism. It is thought to be a mild or early form of hyperparathyroidism. . This condition, is called normocalcemic hyperparathyroidism. Patients with normocalcemic primary hyperparathyroidism are largely asymptomatic. They usually come to medical attention in the context of an evaluation for decreased bone mass. Nevertheless, they often have parathyroid adenomas as well as evidence of metabolic abnormalities and other

endocrine conditions. Kidney stones were found in 28.6% of the women with normocalcemic hyperparathyroidism. It is therefore possible that normocalcemic primary hyperparathyroidism has a phenotype similar to that of the classic form of the disease. In one of the best studies, 41% of patients with normocalcemic primary hyperparathyroidism developed worsening hyperparathyroidism (20% developed high blood calcium levels and the rest developed other problems associated with primary hyperparathyroidism like worsening bone strength). It is unclear whether all patients with normocalcemic primary hyperparathyroidism require parathyroidectomy or if there is only a certain subgroup that benefit. However, research has shown that blood calcium and PTH levels typically become normal after successful parathyroidectomy.

Subclinical Cushing's Syndrome:

Subclinical Cushing's Syndrome occurs in patients bearing clinically inapparent adrenal adenoma secreting cortisol in an autonomous and unregulated way that is not fully restrained by pituitary feedback. Since many patients with clinically nonfunctioning incidentaloma are exposed to a chronic, even if only minimal to mild, cortisol excess, it is biologically plausible to anticipate that they should suffer, at least to some extent, from the classic long-term consequences of overt Cushing's syndrome, such as arterial hypertension, obesity, or diabetes. Evolution of silent hypercortisolism to the overt clinical syndrome occurs rarely, while appearance of silent biochemical alterations was reported in a percentage ranging from 0% to 11% across different studies. Data are insufficient to indicate the superiority of a surgical or nonsurgical approach to manage patients with subclinical hyperfunctioning adrenal cortical adenomas.

Subclinical Addison's Disease:

Adrenal autoantibodies causing primary adrenal insufficiency appear months to years before the appearance of clinical signs of adrenal insufficiency and a pre-clinical phase of the disease can be recognized. Factors increase significantly the risk of progression towards clinical adrenal insufficiency include:

- Male gender
- Presence of other concomitant autoimmune diseases
- Impaired low-dose ACTH stimulation test (LDT)
- High 21OHAb titre.

Corticosteroid treatment can induce long-term remission of subclinical adrenal insufficiency and prevent the onset of the clinical phase of the disease.

Pituitary Incidentaloma:

Pituitary Incidentaloma is defined as a sellar mass discovered by CT or MRI in the absence of any symptoms or clinical findings suggestive of a pituitary disease. The prevalence of pituitary incidentalomas found by MRI is about 10% and most are microadenomas. Most patients with pituitary incidentalomas have no symptoms. Adenomas can be symptomatic due to either hormonal hypersecretion or, in cases of large lesions, due to mass effects (hypopituitarism, optic nerve pressure, neurologic defects). Therapy is indicated for tumours that are found to be hypersecreting. Therefore, prolactinomas would generally be treated with dopamine agonists and those producing GH or ACTH would be treated with surgery. For tumours that do not over-secrete these hormones, the indications for surgery are based initially on mass effects of the tumours and subsequently on tumour size enlargement.