MINIREVIEWS

Non-medicalization of medical science: Rationalization for future

Madhukar Mittal, Parth Jethwani, Dukhabandhu Naik, MK Garg

Madhukar Mittal, Parth Jethwani, MK Garg, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences Jodhpur, Jodhpur 342005, India

Dukhabandhu Naik, Department of Endocrinology and Metabolism, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry 605006, India

Corresponding author: Madhukar Mittal, MBBS, MD, DM, FACE, Additional Professor, Department of Endocrinology and Metabolism, All India Institute of Medical Sciences Jodhpur, Basni hase 2, Jodhpur 342005, India. mittalspace@gmail.com

Abstract

As we delve into the intricacies of human disease, millions of people continue to be diagnosed as having what are labelled as pre-conditions or sub-clinical entities and may receive treatments designed to prevent further progression to clinical disease, but with debatable impact and consequences. Endocrinology is no different, with almost every organ system and associated diseases having subclinical entities. Although the expansion of these "grey" pre-conditions and their treatments come with a better understanding of pathophysiologic processes, they also entail financial costs and drug adverse-effects, and lack true prevention, thus refuting the very foundation of Medicine laid by Hippocrates "Primum non nocere" (Latin), *i.e.,* do no harm. Subclinical hypothyroidism, prediabetes, osteopenia, and minimal autonomous cortisol excess are some of the endocrine preclinical conditions which do not require active pharmacological management in the vast majority. In fact, progression to clinical disease is seen in only a small minority with reversal to normality in most. Giving drugs also does not lead to true prevention by changing the course of future disease. The goal of the medical fraternity thus as a whole should be to bring this large chunk of humanity out of the hospitals towards leading a healthy lifestyle and away from the label of a medical disease condition.

Key Words: Prediabetes; Subclinical hypothyroidism; Osteopenia; Mild autonomous cortisol secretion; Pre-clinical; Medicalization

Core Tip: In this article we discuss several pre-clinical conditions (subclinical hypothyroidism, pre-diabetes, osteopenia, and minimal autonomous cortisol excess), highlighting the futility of early treatment which may not alter the course of future disease. The medical community needs to exercise restraint with pharmacological measures where changes in lifestyle could play a more decisive role in leading a healthy life. Although the expansion of these "grey" pre-conditions and their treatments come with a better understanding of pathophysiologic processes, they also entail financial costs and drug adverse-effects, and lack true prevention, thus refuting the very foundation of Medicine laid by Hippocrates "Primum non nocere" (Latin), *i.e.*, do no harm.

INTRODUCTION

Background

It was David Humes, who more than 250 years ago had discerningly said that "It is impossible to separate the chance of good from the risk of ill", an adage that holds even more meaning today than ever before. In today's era of rapid progress in medical science, the lines have been blurred between "ease" and "dis-ease" with not only medical terms for pre-clinical medical conditions but also various pharmacological treatments being encouraged to "prevent" the development of clinical diseases. The rationale for such treatments remains debatable and controversial.

The concept of medicalization dates back to 1968 when Zola[1] (1972) defined medicalization as "an effective means of social control". Thereafter, Conrad, one of the pioneers of medicalization, defined it as a "process by which non-medical problems become defined and treated as medical problems, usually in terms of illness and disorders"[2]. As a continually evolving term over decades, medicalization can range from sexuality to garden variety mood disturbances, from childbirth to menopause, from cancer to ageing, blurring the lines between physiological and disease states. While physicians' social movements used to be at the crux of medicalization when it was first introduced as a concept in the 1970s, the major players driving medicalization today have been the pharmaceutical and biotechnology industries, posing ethical concerns. The other main reason is the urge to find something "new" or target newer/higher/lower goals in therapeutics by medical scientists, leading to a flurry of pre-clinical labels to almost every chronic disease.

In this article we discuss a few of these pre-clinical conditions [subclinical hypothyroidism, pre-diabetes, osteopenia, and minimal autonomous cortisol excess (MACS)], highlighting the futility of overtreatment which may be variable early in the course. The medical community needs to exercise restraint with pharmacological measures where changes in lifestyle could play a more decisive role in leading a healthy life.

SEARCH STRATEGY

The following databases were used to identify the relevant studies: PubMed/Medline, Scopus, and Cochrane databases. We also applied RCA (Reference Citation Analysis) to further enhance our search results. All the databases were searched from their inception till March 10, 2022. We did a search again and the search was extended up till June 10, 2022 to look for any additional articles. Keywords used were mainly related to the topics of interest including "prediabetes" or "impaired fasting glucose" or "impaired glucose tolerance", "subclinical hypothyroidism", "osteopenia" or "low bone mass", and "mild autonomous cortisol excess". Reference lists of review articles and guidelines were also scanned for potential articles for inclusion. There was no restriction for study design and language (where English language translation was available). All articles related to non-medicalization were reviewed and those relevant to the topics of interest were considered for inclusion in this scoping review.

MACS

MACS is defined as adrenocorticotropic hormone independent cortisol excess often without clinical signs and symptoms of Cushing's syndrome. Previously referred to with terms including "subclinical Cushing's syndrome", "preclinical Cushing's syndrome", and "subclinical hypercortisolism", currently the European Society of Endocrinology/European Network for the Study of Adrenal Tumors has suggested the use of the term "minimal autonomous cortisol excess" which is universally used[3]. The

term was first introduced as "Pre-clinical Cushing's syndrome" by Charbonnel and coworkers in 1981 [4]. The entity has since made rapid strides and undergone major changes with respect to its understanding, nomenclature, and definitions used for diagnosis.

Approximately 0.3% of adrenal incidentalomas present with Cushing's syndrome[5]. MACS is diagnosed in 5%-48% of patients with incidentally discovered adrenal tumors following evaluation in endocrine clinics[6,7]. The diagnosis of MACS is made in patients with adrenal incidentaloma by an abnormal 1-mg dexamethasone suppression test (DST) with absent stigmata of Cushing's syndrome. The 1-mg DST has been recommended by current recommendations to have the highest sensitivity for diagnosing MACS[3,8]. However, the diagnosis requires exclusion of potential causes of physiological hypercortisolism such as obesity, diabetes, and anxiety/depression. These have also been described as comorbidities associated with MACS and can act as potential confounders in diagnosis.

In a recent systemic review and meta-analysis done by Elhassan *et al*[9] involving more than 4000 patients with benign adrenal incidentalomas, the prevalence of hypertension, obesity, dyslipidemia, and type 2 diabetes in the MACS sub-group was 64%, 41%, 34%, and 28% respectively. This prevalence of dyslipidemia and obesity was almost similar to that of non-functioning adrenal tumors (NFAT) and only hypertension and diabetes were more common in the MACS subgroup. Although hypertension, dyslipidemia, and diabetes were likely to worsen in the MACS sub-group on follow-up, progressive worsening is the *sine qua non* in most chronic conditions. The results have been conflicting with cardiovascular events being prevalent in non-functioning adrenal tumors at baseline (8.7% *vs* 6.3%), and new cardiovascular events developing in MACS than NFAT (15.5% *vs* 6.4%). On top of it, the mortality rates were similar between the two groups despite these differences in metabolic complications. This would mandate a cautionary approach to managing "mild" hypercortisolism based on no difference shown in mortality outcomes, thus putting in doubt the benefit of any intervention at this so-called pre-clinical stage

Patients with MACS have also been found to carry a risk of osteoporosis and mostly asymptomatic vertebral fractures (46%-82%), as compared to 13%-23% of patients with non-functioning adrenal incidentalomas[10]. A study done by Goh *et al*[11] followed 101 patients with benign adrenal adenomas over a 3-year follow-up period. Ninety-two patients had a diagnosis of non-functioning adenomas while nine had a diagnosis of MACS defined as an abnormal 24-h urinary free cortisol and 1mg-DST. After 3 years (range 2.9-4.7 years), four of the nine patients with MACS showed normalization of cortisol parameters (44%), and five of the 92 non-functional AI patients developed MACS (5%). Nearly half of the patients with MACS had normalization of biochemical parameters on follow-up. Whether the initial diagnosis was because of a false-positive test in the first place, or a spontaneous reversal of the cortisol excess, the more important fact is that only 9% of patients had MACS initially and more than half of them normalized on follow-up. Additionally, the risk of progression to overt Cushing's remains very low (< 1%) in patients with MACS, as has been uniformly reported across multiple studies[12-14]. Hence, this should prompt a more vigilant interpretation of any results which imply a higher risk for complications in MACS. This also suggests that caution be exercised with regard to diagnostic interpretation and adopting invasive management decisions.

There remains a need to establish the benefits of adrenalectomy with regard to mortality, quality of life, and potential reversal of these comorbidities in light of the doubtful clinical impact of MACS. A meta-analysis done by Bancos *et al*[15] involving retrospective studies with heterogeneous definitions of MACS showed improvement in hypertension (relative risk [RR] = 11, 95%CI: 4.3–27.8) and diabetes mellitus (RR = 3.9, 95%CI: 1.5–9.9), but not dyslipidemia (RR = 2.6, 95%CI: 0.97–7.2) or obesity (RR = 3.4, 95%CI: 0.95–12) when compared with conservative management. A study done by Salcuni *et al*[16] found a 30% vertebral fracture risk reduction with surgical *vs* conservative management (odds ratio = 0.7, 95%CI: 0.01-0.05, *P* = 0.008). There have been few studies on the potential use of Mifepristone and Metyrapone in MACS demonstrating beneficial effects on several metabolic parameters[17,18].

All such evidence is largely based on small, heterogeneous studies with inconsistent definitions of MACS and comorbidities as well as degrees of improvement. With the knowledge that half of MACS cases return to normalcy (nonfunctional status), < 1% progress to Cushing's syndrome, and a major surgery involves risks and morbidity, publication bias for positive results certainly calls into question this medicalization.

Moreover, differences in assay factors and the presence of significant comorbidities may lead to possible false-positive results leading to misclassification of patients and adding to bias.

The 2016 European guidelines for the management of adrenal incidentaloma currently suggest an individualized approach. They do recommend surgical management in patients with post-dexamethasone cortisol > 138 nmol/L (> 5 μg/dL) and the presence of at least two comorbidities potentially related to cortisol excess (*e.g.,* type 2 diabetes, hypertension, obesity, and osteoporosis), of which at least one is poorly controlled by medical measures. One needs to weigh the risks and morbidity associated with an adrenal surgery with the perceived benefits. A causal link between MACS and these comorbidities has not been unequivocally established, and these comorbidities can usually be efficaciously managed with medical treatment. Robust randomized trials comparing intensive medical therapy and adrenalectomy, with consistent definitions, appropriately defined endpoints, and a longer duration of follow-up, may bust the myth of operating on MACS.

Subclinical hypothyroidism

As an entity which has been in vogue over the past few decades, subclinical hypothyroidism is essentially a biochemical diagnosis, defined as an elevated thyrotropin (TSH) level with a fT4 level that is within the population specific range.

The prevalence of overt hypothyroidism ranges from 0.2%-5.3%[19] while the prevalence of subclinical hypothyroidism varies from 4.3% to 15% (3× to 150×), with a multitude of factors affecting incidence, including female gender, age, and iodine status[20]. Serum TSH levels in subclinical hypothyroidism have been classified into two categories ranging from the upper limit of normal to 10 and 10 or higher. What is interesting to note is the fact that more than 90% of patients fall in the earlier bracket. Even more striking is the fact that the risk of progression to overt hypothyroidism is only 2% per year in the absence of thyroid peroxidase (TPO) antibodies and 4% per year in the presence of TPO antibodies. As many as two-thirds (approximately 60%) of these individuals see their TSH levels return to the normal range without treatment[21]. Simply put, treating 100 patients for hypothyroidism with TSH between 4-10 mU/mL will potentially avoid progression to overt hypothyroidism in 2-4 patients while what they add on to are unnecessary multiple clinic visits, treatment costs, polypharmacy, and modification of daily habits including taking the tablet 30-60 min before a meal in the rest. The question that matters "is it really worth it?" and are we wasting 96% of our efforts? Would it not be prudent to wait for identifying and then treating only those who actually progress to overt hypothyroidism unless there are significant immediate medical concerns which may benefit from treatment as in infertility or in pregnant females?

There are a number of factors affecting TSH levels. TSH levels tend to follow a circadian fluctuation with nadir levels in the afternoon and only 30% having higher levels in the evening and night. This TSH peak may also be altered in night-shift workers and those with irregular sleep patterns, following vigorous exercise, and mood disorders. Moreover, although population specific reference ranges have been defined for fT4 and TSH concentrations, the intra-individual hypothalamic-pituitary axis set point is largely genetically determined and is minutely sensitive to changes in thyroxine concentrations, which despite being within the population specific range, may be enough to result in an increased TSH concentration. Furthermore, due to alterations in the hypothalamic-pituitary TSH set point, there is a trend towards elevated TSH concentrations with advancing age which is a physiological change. Besides this, there are several conditions which should be ruled out before making a diagnosis of subclinical hypothyroidism (SCH)[22] (Table 1).

Taking these factors into account, the guidelines clearly mention that a diagnosis of subclinical hypothyroidism should be made following confirmation with a repeat TSH and T4 measurement[23] and even when reconfirmed on second testing, only a subset may need treatment. However, one-third of the people are offered treatment after a single TSH measurement making them "patients" and making levothyroxine one of the leading prescriptions worldwide[24].

Symptoms and quality of life: With regard to symptomatology, around one in three patients with subclinical hypothyroidism are asymptomatic. Symptoms when present, tend to predominantly be fatigue, muscle weakness, and cold intolerance. However, around 20%-25% of patients with normal TSH levels report these symptoms. A meta-analysis done by Feller *et al*[25] in 2018 on quality of life showed no difference in hypothyroid symptoms (16.7 *vs* 16.5) or fatigue (28.6 *vs* 29) as assessed using the ThyPRO self-reported instrument (scale 0–100, lower better), or in health related quality of life, depression, cognitive function, or muscle strength. About treatment on the various aspects of hypothyroidism, the largest trial done to date, the TRUST trial, did not demonstrate any effect of levothyroxine on the coprimary outcomes of hypothyroid symptoms and fatigue scores after 12 mo of therapy nor on the secondary outcomes of quality of life, handgrip strength, cognitive function, blood pressure, weight, body mass index (BMI), waist circumference, or carotid plaque thickness[26].

Cardiovascular risk: Amongst the various organ systems that thyroid hormone does play a role in, its effects on the cardiovascular system have been evaluated most extensively. Multiple studies have found that surrogate markers of cardiovascular function (such as left ventricular diastolic function) and lipid profile deteriorate with subclinical hypothyroidism[27,28]. However, while these observations seem to suggest that raised TSH levels may be associated with an increased risk of adverse cardiovascular outcomes, such has not been the case in multiple randomized trials. Subclinical hypothyroidism was not associated with an increased risk of atrial fibrillation, heart failure, stroke, coronary heart disease events, mortality from coronary heart disease, or overall mortality compared with euthyroid individuals in an individual patient meta-analysis performed by the Thyroid Studies Collaboration[29-32]. There are limited randomized clinical trials with sufficient power to examine the impact of thyroid hormone therapy on cardiovascular events, and the TRUST study found that treatment of SCH did not impact the incidence of cardiovascular events within 1 year after initiation of therapy[26].

Treatment: Current guidelines recommend that all individuals with subclinical hypothyroidism would not benefit from treatment and clinicians need to weigh other factors when deciding on treatment[33-35]. Treatment guidelines for subclinical hypothyroidism have been summarized[36-38]. To conclude, there is significant evidence to suggest that subclinical hypothyroidism remains an entity which is

Table 1 Causes of elevated thyrotropin levels

Transient increase in TSH	Permanent increase in TSH
Non-thyroidal illness	Assay interference
Thyroiditis	TSH hormone resistance
Medications: Amiodarone and Lithium	Adrenal insufficiency
Lack of adherence to treatment	Obesity

TSH: Thyrotropin.

misdiagnosed and largely over-treated, and there is a need to improve adherence to the guidelines (Table 2) with periodic reassessment of symptoms, with discontinuation of treatment if and when no benefit becomes evident.

Prediabetes

Pre-diabetes, a term developed to pre-empt the progression to diabetes, represents an intermediate state of hyperglycemia. Varying definitions have been used by the World Health Organization (WHO) and the American Diabetes Association (ADA) to define prediabetes, classifying them into impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) depending on fasting plasma glucose levels and 2-h plasma glucose levels after a 75 g oral glucose tolerance test. ADA, in addition, uses hemoglobin A1c (HbA1c) too to classify diabetes[39,40].

The worldwide prevalence of diabetes ranges from 6% to 10.5% in adults[41,42] while the prevalence of pre-diabetes ranges from 5.5% to around 50%[43] depending on the ethnicity and definitions used to define pre-diabetes (Table 3). The yearly conversion rate from pre-diabetes to diabetes is 5%-20%, with rates ranging from 4%-6% for isolated IGT, 6%-9% for isolated IFG, and 15%-19% for those with both IFG and IGT[44]. The reversal rates vary from 45% for individuals with IFG, 37% for individuals with IGT, and 17% for individuals with impaired HbA1c levels[45].

Complications of pre-diabetes: The strongest evidence for pre-diabetes comes with cardiovascular complications[46]. In a meta-analysis done by Huang *et al*[47], IFG, IGT, and HbA1c were independently associated with an increased risk of composite cardiovascular outcomes, coronary heart disease, stroke, and all-cause mortality. In a meta-analysis done by Echouffo-Tcheugui *et al*[48], pre-diabetes was associated with a moderately increased risk of CKD. Several studies have shown similar results with increased rates of micro-albuminuria and progression to chronic kidney disease in prediabetes[49-51]. Pre-diabetes also has been associated with an increased prevalence of diabetic neuropathy, especially autonomic involvement, and increased risk of diabetic retinopathy[52,53].

Treatment: Multiple randomized control trials including the diabetes prevention program (DPP)[54], the Finnish diabetes prevention study[55], and the Da Qing diabetes prevention study[56] demonstrated that lifestyle/behavioral therapy is highly effective in preventing progression to type 2 diabetes. In a recent meta-analysis, lifestyle interventions for obese or overweight individuals with pre-diabetes led to a reduced incidence of diabetes[57]. The DPP for instance demonstrated that an intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58%. To prevent one case of diabetes during a period of 3 years, 6.9 persons would have to participate in the lifestyle-intervention program, and 13.9 would have to receive metformin. The ADA currently recommends lifestyle modification for pre-diabetes with a target of 7% weight loss and 150 min/wk of moderate intensity physical activity[58].

While weight loss does lead to a definite reduction in incident type 2 diabetes, it often comes with the challenge of sustaining it long-term[59]. Multiple pharmacological agents have been evaluated with the strongest evidence and long-term safety favoring metformin. In the Indian Diabetes Prevention Programme (IDPP-1) study, metformin and lifestyle intervention reduced diabetes risk similarly at 30 mo although the lifestyle intervention in the Indian DPP-1 was less effective than the DPP[60]. The ADA currently recommends that metformin should be considered in those with BMI ≥ 35 kg/m^2, those aged < 60 years, and women with prior gestational diabetes mellitus[58].

While current evidence does suggest the effectiveness of treatment modalities for the prevention of pre-diabetes to diabetes, the long-term effects on microvascular and macrovascular complications remain debatable. Moreover, although pharmacotherapy has been found to be beneficial in preventing type 2 diabetes, questions regarding the starting and endpoint of therapy, long-term safety of other potential drugs, and economic considerations regarding its cost-effectiveness and health benefits remain unanswered.

Shahraz *et al*[61] using NHANES data showed that a widely promoted web-based risk test by ADA and AMA would label more than 73 million Americans, including more than 80% of those older than 60 years, as being at high risk for "prediabetes", thus elegantly demonstrating how common conditions can

Table 2 Guideline recommendations for treatment of subclinical hypothyroidism			
Degree of subclinical hypothyroidism	ATA 2012[36]	ETA 2013[37]	NICE 2019[38]
TSH > 10 mIU/L	Levothyroxine should be considered. (Grade B)	Younger patients (< 65 to 70 yr): Treatment with levothyroxine is recommended, even in the absence of symptoms. (Grade 2); Older patients (> 70 yr): Treatment with levothyroxine should be considered if clear symptoms of hypothyroidism are present or if the risk of vascular events is high. (Not a graded recommendation, but part of the treatment algorithm)	All adults (on 2 occasions, 3 mo apart) consider treatment.
TSH: ULN to 10 mIU/L	Treatment should be considered on the basis of individual factors (*i.e.*, symptoms suggestive of hypothyroidism, a positive test for antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases). (Grade B, because of a lack of randomized, controlled trials)	Younger patients (< 65 to 70 yr): A trial period of treatment with levothyroxine should be considered when symptoms suggestive of hypothyroidism are present. (Grade 2); Older patients (especially > 80 to 85 yr): Careful follow-up with a wait-and-see strategy, generally avoiding hormonal treatment, is recommended. (Grade 3)	Age < 65 years (on 2 occasions, 3 mo apart): Consider a 6-mo trial of levothyroxine if symptoms are present.

ATA: American Thyroid Association; ETA: European Thyroid Association; NICE: National Institute for Health and Care Excellence; TSH: Thyrotropin.

Table 3 Criteria for prediabetes		
	WHO[39]	ADA[40]
FPG (mg/dL)	110-125	100-125
2-h plasma glucose (mg/dL)	140-199	140-199
HbA1c (%)		5.7-6.4

ADA: American Diabetes Association; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; WHO: World Health Organization.

be "medicalized".

Osteopenia

Osteopenia, a term which came into being by the WHO in 1992, was initially "meant to indicate the emergence of a problem without having any diagnostic or therapeutic significance". The WHO currently defines osteopenia as a bone mineral density (BMD) T score that is higher than −2.5 but less than −1.0[62,63].

The prevalence of osteoporosis ranges from 2% to 26.3%[64] while that of osteopenia is two to three times higher, varying from 54% to 80%[65]. Because osteopenia is so much more prevalent than osteoporosis, the majority of fractures occur in women with osteopenia. In the National Osteoporosis risk assessment study which involved 149542 postmenopausal women followed for 1 year, the gross disparity in the proportion of women with osteopenia and osteoporosis (39% *vs* 6%) meant that more fractures were observed among women with osteopenia despite that they had a lower risk for the same.

When we look at the temporal transition of osteopenia to osteoporosis in a study done by Gourlay *et al*[66] which included 3702 women with osteopenia, the investigators estimated the time for 10% of the women to transition to osteoporosis before having a hip or clinical vertebral fracture. Women were stratified into three subgroups: Mild osteopenia (T score from −1.01 to −1.49), moderate osteopenia (T score from −1.50 to −1.99), and severe osteopenia (T score from −2.00 to −2.49). For 10% of the women to transition to osteoporosis, it took 17 years for those with mild osteopenia, 5 years for those with moderate osteopenia, and 1 year for those with severe osteopenia. Moreover, there was no difference in time needed to transition to osteoporosis among women with normal bone density and mild osteopenia.

Hillier *et al*[67] performed a study including a large cohort of women aged 65 years and older with osteopenia at baseline; 4.7 and 15.7% of these women developed hip and a major osteoporotic fracture, respectively, within 10 years. The corresponding values were 1.2% and 6.3% for women with normal BMD and 14.3% and 30% for women with osteoporosis.

While lifestyle measures along with appropriate intake of calcium and vitamin D can be uniformly recommended to all women with osteopenia, pharmacological treatment remains largely debatable[68, 69]. A variety of algorithms and clinical tools such as the fracture risk assessment tool have been developed to enable physicians in stratifying women with osteopenia and decide on potential indications of treatment. Most trials evaluating the efficacy of these agents involve women with

Table 4 Criteria for defining osteopenia

Category	Definition	Treatment recommendation
"Moderate risk", Endocrine Society guidelines 2019[74]	Clinical: No prior hip or spine fractures, BMD T-score at the hip and spine both above -2.5, 10-yr hip fracture risk < 3% or risk of major osteoporotic fractures < 20%	Reassess fracture risk in 2-4 yr. Country-specific guidelines for treatment
ISBMR guidelines 2021 [75]	BMD T-score between -1.0 and -2.5 at the femoral neck or lumbar spine, 10-yr probability of a hip fracture ≥ 3.5%, or a 10-yr probability of a major osteoporosis-related fracture ≥ 10.5% based on the FRAX tool (based on limited data in Indians)	Advisable to initiate treatment

BMD: Bone mineral density.

osteoporosis or prevalent vertebral fractures with fewer trials in osteopenic women. In the fracture intervention trial, alendronate was not associated with a reduced risk of sustaining a vertebral fracture among women with a T score between −1.6 and −2.5 (hazard ratio = 0.8; 95%CI: 0.3–2.1)[70]. In a RCT done by McCloskey *et al*[71], the number needed to treat (NNT) to prevent the occurrence of one clinical fracture was three and a half times higher among women with T>-2.5 than women with osteoporosis (NNT = 66 *vs* 19) despite a similar RR reduction (22% *vs* 30%). Hence, while RR reduction might appear greater in terms of numbers, it does not quite translate into significant numbers in terms of absolute risk reduction. Cost-effectiveness is another factor that needs to be taken into consideration. Studies done by Schousboe *et al*[72] and Meadows *et al*[73] have assessed the cost-effectiveness of prescribing alendronate among post-menopausal women with osteopenia and found that the drug is not cost-effective. The long duration of treatment, lack of defined endpoints, and the adverse effects associated with long-term use are other factors that need to be considered prior to initiating pharmacological therapy in osteopenia (Table 4)[74,75]. Hence, in the absence of unequivocal clinically and epidemiologically relevant benefits of pharmacotherapy, osteopenia essentially remains a radiological diagnosis in the absence of risk factors for fracture and is probably best managed by periodic monitoring and fracture risk assessment.

Reasons for progressive medicalization

There are many reasons why clinicians may provide more care than is needed. A primary reason is "technology creep". After a new drug or device is approved for use in a condition in which there is a proven benefit, its use often expands to lower-risk groups in which the benefit does not outweigh the risk. Others include payment systems that reward procedures disproportionately compared with talking to patients, expectations of patients who equate testing and interventions with better care, the glamour of technology, the fact that it may be quicker to order a test or write a prescription than explain to a patient why they are not being treated, and defensive medicine[76]. Even if a medical intervention has been shown to provide a clear benefit in selected groups, using it in other groups, especially in those with milder disease or at-risk group for disease, can result in harm.

It is worthwhile to note that providing excessive health care service is most likely to occur in situations in which there is less strong evidence to document the benefit and harms of the service. In fact, editors of *JAMA Internal Medicine* took note of "medicalization" of common conditions, as an area of increasing concern[77]. "Less is More" was a series used to highlight situations in which the overuse of medical care could result in harm and in which less care is likely to result in better health[78]. A comprehensive look at the four pre-clinical conditions is summarized in Table 5.

CONCLUSION

A fine balance between indiscriminate acceptance of medicalization of areas of human existence and blind criticism of new medicalization cases needs to be struck. A reasonable way to look at any chronic non-communicable disease should be to avoid unnecessary medicalization by medical labeling of the "grey zone" preceding a disease. Rather, it should seek to identify people at the highest risk for targeted allocation of limited health care resources and address the lifestyle changes which can improve the overall health of the community. Having a proven therapeutic intervention for a disease does not pre-validate its use in the pre-clinical stage of the same disease and can lead to more harm than good.

The time is more than ripe for paying heed to hard facts and sane logic both for the patient as well as the medical community for treading carefully with regard to early interventions for "preclinical and subclinical" conditions in medical science.

Table 5 Clinical spectrum of preclinical conditions: Looking at hard facts

	Prediabetes	Subclinical hypothyroidism	Osteopenia	MACS
Clinical disease	Diabetes	Overt primary hypothyroidism	Osteoporosis	Cushing's syndrome
Prevalence of preclinical condition	5.5%-53.1%[43], IFG - 6.2%[41], IGT -10.6% [41]	4.3%-15%[20]	54%-80%[65]	5%-48%[6]
Prevalence of clinical condition	10.5%[41]	0.2%-5.3%[19]	2%-26.3%[64]	0.3% of patients with adrenal incidentalomas[5]
Dx criteria	FPG: 100-125, 2-h PPG: 140-199, HbA1C: 5.7-6.4	Elevated TSH level with a fT4 level that is within the population specific range	T-score between -1 to -2.5	Abnormal 1-mg dexamethasone suppression test with absent stigmata of Cushing's disease.
Progression	5%-18.3%[54,55,60]	2%-6%[22]	16% risk of major osteoporotic fracture in 10 years [67]	< 1%[13]
Regression/reversal	19%[54]	60%[21]	Stays static or progresses	2%-44%[6,11]
Long-term sequelae	Microvascular and macrovascular complications of diabetes, Cardiovascular risk	Markers of cardiovascular function (such as left ventricular diastolic function) and lipid profile deteriorate with subclinical hypothyroidism	Fractures	Hypertension, Diabetes, Dyslip-idemia, Osteoporosis
Short-term consequences		Fatigue, muscle weakness, cold intolerance		
Preventive options	Lifestyle and behavioural therapy, drugs	Lifestyle and behavioural therapy, drugs	Lifestyle and behavioural therapy, drugs	Lifestyle and behavioural therapy, drugs, surgery
Pharmacotherapy	Metformin	L-thyroxine	Calcium and vitamin D	Mifepristone, metyrapone
Surgery	-	-	-	Adrenalectomy
True prevention	x	x	x	x
Adverse effects of treatments available	B12 deficiency	Bone loss, cardiac arrhythmias in elderly	Overtreatment can predispose to hypervitaminosis D	Hypocortisolism
Recommendations/Guidelines	Metformin should be considered in those with BMI ≥ 35 kg/m², those aged < 60 yr, and women with prior gestational diabetes mellitus with IGT	TSH > 10 mIU/L, consider treatment; TSH < 10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases	Country-specific guidelines for treatment	Individualized approach to consider patients with 'autonomous cortisol secretion' due to a benign adrenal adenoma and comorbidities potentially related to cortisol excess for adrenal surgery
Grade of recommendation	Level of evidence A[58]	Grade B, BEL 1 (Best evidence rating level)[36]	-	(⊕OOO) Very low level of evidence/recommendation[3]

MACS: Minimal autonomous cortisol excess; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; FPG: Fasting plasma glucose; HbA1C: Hemoglobin A1c; PPG: Photoplethysmography; TSH: Thyrotropin; BMI: Body mass index.

FOOTNOTES

REFERENCES

1   **Zola IK**. Medicine as an institution of social control. *Sociol Rev* 1972; **20**: 487-504 [PMID: 4645802 DOI: 10.1111/j.1467-954x.1972.tb00220.x]

2   Correia T. Revisiting Medicalization: A Critique of the Assumptions of What Counts As Medical Knowledge. Frontiers in Sociology 2017; 2. Available from: https://www.frontiersin.org/article/10.3389/fsoc.2017.00014. Accessed 9 June 2022

3   **Fassnacht M**, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, Dekkers OM. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol* 2016; **175**: G1-G34 [PMID: 27390021 DOI: 10.1530/EJE-16-0467]

4   **Charbonnel B**, Chatal JF, Ozanne P. Does the corticoadrenal adenoma with "pre-Cushing's syndrome" exist? *J Nucl Med* 1981; **22**: 1059-1061 [PMID: 6273512]

5   **Yozamp N**, Vaidya A. Assessment of mild autonomous cortisol secretion among incidentally discovered adrenal masses. *Best Pract Res Clin Endocrinol Metab* 2021; **35**: 101491 [PMID: 33593680 DOI: 10.1016/j.beem.2021.101491]

6   **Delivanis DA**, Athimulam S, Bancos I. Modern Management of Mild Autonomous Cortisol Secretion. *Clin Pharmacol Ther* 2019; **106**: 1209-1221 [PMID: 31206616 DOI: 10.1002/cpt.1551]

7   **Prete A**, Subramanian A, Bancos I, Chortis V, Tsagarakis S, Lang K, Macech M, Delivanis DA, Pupovac ID, Reimondo G, Marina LV, Deutschbein T, Balomenaki M, O'Reilly MW, Gilligan LC, Jenkinson C, Bednarczuk T, Zhang CD, Dusek T, Diamantopoulos A, Asia M, Kondracka A, Li D, Masjkur JR, Quinkler M, Ueland GÅ, Dennedy MC, Beuschlein F, Tabarin A, Fassnacht M, Ivović M, Terzolo M, Kastelan D, Young WF Jr, Manolopoulos KN, Ambroziak U, Vassiliadi DA, Taylor AE, Sitch AJ, Nirantharakumar K, Arlt W; ENSAT EURINE-ACT Investigators*; ENSAT EURINE-ACT Investigators. Cardiometabolic Disease Burden and Steroid Excretion in Benign Adrenal Tumors: A Cross-Sectional Multicenter Study. *Ann Intern Med* 2022; **175**: 325-334 [PMID: 34978855 DOI: 10.7326/M21-1737]

8   **Sherlock M**, Scarsbrook A, Abbas A, Fraser S, Limumpornpetch P, Dineen R, Stewart PM. Adrenal Incidentaloma. *Endocr Rev* 2020; **41** [PMID: 32266384 DOI: 10.1210/endrev/bnaa008]

9   **Elhassan YS**, Alahdab F, Prete A, Delivanis DA, Khanna A, Prokop L, Murad MH, O'Reilly MW, Arlt W, Bancos I. Natural History of Adrenal Incidentalomas With and Without Mild Autonomous Cortisol Excess: A Systematic Review and Meta-analysis. *Ann Intern Med* 2019; **171**: 107-116 [PMID: 31234202 DOI: 10.7326/M18-3630]

10   **Chiodini I**, Viti R, Coletti F, Guglielmi G, Battista C, Ermetici F, Morelli V, Salcuni A, Carnevale V, Urbano F, Muscarella S, Ambrosi B, Arosio M, Beck-Peccoz P, Scillitani A. Eugonadal male patients with adrenal incidentalomas and subclinical hypercortisolism have increased rate of vertebral fractures. *Clin Endocrinol (Oxf)* 2009; **70**: 208-213 [PMID: 18547342 DOI: 10.1111/j.1365-2265.2008.03310.x]

11   **Goh Z**, Phillips I, Hunt PJ, Soule S, Cawood TJ. Three-year follow up of adrenal incidentalomas in a New Zealand centre. *Intern Med J* 2020; **50**: 350-356 [PMID: 31058434 DOI: 10.1111/imj.14332]

12   **Libè R**, Dall'Asta C, Barbetta L, Baccarelli A, Beck-Peccoz P, Ambrosi B. Long-term follow-up study of patients with adrenal incidentalomas. *Eur J Endocrinol* 2002; **147**: 489-494 [PMID: 12370111 DOI: 10.1530/eje.0.1470489]

13   **Barzon L**, Sonino N, Fallo F, Palu G, Boscaro M. Prevalence and natural history of adrenal incidentalomas. *Eur J Endocrinol* 2003; **149**: 273-285 [PMID: 14514341 DOI: 10.1530/eje.0.1490273]

14   **Nieman LK**. Update on subclinical Cushing's syndrome. *Curr Opin Endocrinol Diabetes Obes* 2015; **22**: 180-184 [PMID: 25887388 DOI: 10.1097/MED.0000000000000159]

15   **Bancos I**, Alahdab F, Crowley RK, Chortis V, Delivanis DA, Erickson D, Natt N, Terzolo M, Arlt W, Young WF Jr, Murad MH. THERAPY OF ENDOCRINE DISEASE: Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: a systematic review and meta-analysis. *Eur J Endocrinol* 2016; **175**: R283-R295 [PMID: 27450696 DOI: 10.1530/EJE-16-0465]

16   **Salcuni AS**, Morelli V, Eller Vainicher C, Palmieri S, Cairoli E, Spada A, Scillitani A, Chiodini I. Adrenalectomy reduces the risk of vertebral fractures in patients with monolateral adrenal incidentalomas and subclinical hypercortisolism. *Eur J Endocrinol* 2016; **174**: 261-269 [PMID: 26630908 DOI: 10.1530/EJE-15-0977]

17   **Belokovskaya R**, Ravikumar A, Arumugam D, Izadmehr S, Goddard GM, Geer EB, Levine AC. MIFEPRISTONE TREATMENT FOR MILD AUTONOMOUS CORTISOL SECRETION DUE TO ADRENAL ADENOMAS: A PILOT STUDY. *Endocr Pract* 2019; **25**: 846-853 [PMID: 31070948 DOI: 10.4158/EP-2019-0047]

18   **Debono M**, Harrison RF, Chadarevian R, Gueroult C, Abitbol JL, Newell-Price J. Resetting the Abnormal Circadian Cortisol Rhythm in Adrenal Incidentaloma Patients With Mild Autonomous Cortisol Secretion. *J Clin Endocrinol Metab* 2017; **102**: 3461-3469 [PMID: 28911138 DOI: 10.1210/jc.2017-00823]

19   **Taylor PN**, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, Okosieme OE. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* 2018; **14**: 301-316 [PMID: 29569622 DOI: 10.1038/nrendo.2018.18]

20   **Calsolaro V**, Niccolai F, Pasqualetti G, Calabrese AM, Polini A, Okoye C, Magno S, Caraccio N, Monzani F. Overt and

Subclinical Hypothyroidism in the Elderly: When to Treat? *Front Endocrinol (Lausanne)* 2019; **10**: 177 [PMID: 30967841 DOI: 10.3389/fendo.2019.00177]

21   **Biondi B**, Cappola AR, Cooper DS. Subclinical Hypothyroidism: A Review. *JAMA* 2019; **322**: 153-160 [PMID: 31287527 DOI: 10.1001/jama.2019.9052]

22   **Peeters RP**. Subclinical Hypothyroidism. *N Engl J Med* 2017; **376**: 2556-2565 [PMID: 28657873 DOI: 10.1056/NEJMcp1611144]

23   **Jonklaas J**, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, Cooper DS, Kim BW, Peeters RP, Rosenthal MS, Sawka AM; American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid* 2014; **24**: 1670-1751 [PMID: 25266247 DOI: 10.1089/thy.2014.0028]

24   **Taylor PN**, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R, Hamilton W, Okosieme O, Panicker V, Thomas SL, Dayan C. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. *JAMA Intern Med* 2014; **174**: 32-39 [PMID: 24100714 DOI: 10.1001/jamainternmed.2013.11312]

25   **Feller M**, Snel M, Moutzouri E, Bauer DC, de Montmollin M, Aujesky D, Ford I, Gussekloo J, Kearney PM, Mooijaart S, Quinn T, Stott D, Westendorp R, Rodondi N, Dekkers OM. Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism: A Systematic Review and Meta-analysis. *JAMA* 2018; **320**: 1349-1359 [PMID: 30285179 DOI: 10.1001/jama.2018.13770]

26   **Stott DJ**, Rodondi N, Kearney PM, Ford I, Westendorp RGJ, Mooijaart SP, Sattar N, Aubert CE, Aujesky D, Bauer DC, Baumgartner C, Blum MR, Browne JP, Byrne S, Collet TH, Dekkers OM, den Elzen WPJ, Du Puy RS, Ellis G, Feller M, Floriani C, Hendry K, Hurley C, Jukema JW, Kean S, Kelly M, Krebs D, Langhorne P, McCarthy G, McCarthy V, McConnachie A, McDade M, Messow M, O'Flynn A, O'Riordan D, Poortvliet RKE, Quinn TJ, Russell A, Sinnott C, Smit JWA, Van Dorland HA, Walsh KA, Walsh EK, Watt T, Wilson R, Gussekloo J; TRUST Study Group. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. *N Engl J Med* 2017; **376**: 2534-2544 [PMID: 28402245 DOI: 10.1056/NEJMoa1603825]

27   **Chen X**, Zhang N, Cai Y, Shi J. Evaluation of left ventricular diastolic function using tissue Doppler echocardiography and conventional doppler echocardiography in patients with subclinical hypothyroidism aged <60 years: a meta-analysis. *J Cardiol* 2013; **61**: 8-15 [PMID: 23084577 DOI: 10.1016/j.jjcc.2012.08.017]

28   **Liu XL**, He S, Zhang SF, Wang J, Sun XF, Gong CM, Zheng SJ, Zhou JC, Xu J. Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. *Med Sci Monit* 2014; **20**: 1432-1441 [PMID: 25124461 DOI: 10.12659/MSM.891163]

29   **Rodondi N**, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E, Gussekloo J; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA* 2010; **304**: 1365-1374 [PMID: 20858880 DOI: 10.1001/jama.2010.1361]

30   **Gencer B**, Collet TH, Virgini V, Bauer DC, Gussekloo J, Cappola AR, Nanchen D, den Elzen WP, Balmer P, Luben RN, Iacoviello M, Triggiani V, Cornuz J, Newman AB, Khaw KT, Jukema JW, Westendorp RG, Vittinghoff E, Aujesky D, Rodondi N; Thyroid Studies Collaboration. Subclinical thyroid dysfunction and the risk of heart failure events: an individual participant data analysis from 6 prospective cohorts. *Circulation* 2012; **126**: 1040-1049 [PMID: 22821943 DOI: 10.1161/CIRCULATIONAHA.112.096024]

31   **Chaker L**, Baumgartner C, den Elzen WP, Ikram MA, Blum MR, Collet TH, Bakker SJ, Dehghan A, Drechsler C, Luben RN, Hofman A, Portegies ML, Medici M, Iervasi G, Stott DJ, Ford I, Bremner A, Wanner C, Ferrucci L, Newman AB, Dullaart RP, Sgarbi JA, Ceresini G, Maciel RM, Westendorp RG, Jukema JW, Imaizumi M, Franklyn JA, Bauer DC, Walsh JP, Razvi S, Khaw KT, Cappola AR, Völzke H, Franco OH, Gussekloo J, Rodondi N, Peeters RP; Thyroid Studies Collaboration. Subclinical Hypothyroidism and the Risk of Stroke Events and Fatal Stroke: An Individual Participant Data Analysis. *J Clin Endocrinol Metab* 2015; **100**: 2181-2191 [PMID: 25856213 DOI: 10.1210/jc.2015-1438]

32   **Baumgartner C**, da Costa BR, Collet TH, Feller M, Floriani C, Bauer DC, Cappola AR, Heckbert SR, Ceresini G, Gussekloo J, den Elzen WPJ, Peeters RP, Luben R, Völzke H, Dörr M, Walsh JP, Bremner A, Iacoviello M, Macfarlane P, Heeringa J, Stott DJ, Westendorp RGJ, Khaw KT, Magnani JW, Aujesky D, Rodondi N; Thyroid Studies Collaboration. Thyroid Function Within the Normal Range, Subclinical Hypothyroidism, and the Risk of Atrial Fibrillation. *Circulation* 2017; **136**: 2100-2116 [PMID: 29061566 DOI: 10.1161/CIRCULATIONAHA.117.028753]

33   **Bekkering GE**, Agoritsas T, Lytvyn L, Heen AF, Feller M, Moutzouri E, Abdulazeem H, Aertgeerts B, Beecher D, Brito JP, Farhoumand PD, Singh Ospina N, Rodondi N, van Driel M, Wallace E, Snel M, Okwen PM, Siemieniuk R, Vandvik PO, Kuijpers T, Vermandere M. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. *BMJ* 2019; **365**: l2006 [PMID: 31088853 DOI: 10.1136/bmj.l2006]

34   **Poppe K**, Bisschop P, Fugazzola L, Minziori G, Unuane D, Weghofer A. 2021 European Thyroid Association Guideline on Thyroid Disorders prior to and during Assisted Reproduction. *Eur Thyroid J* 2021; **9**: 281-295 [PMID: 33718252 DOI: 10.1159/000512790]

35   **Biondi B**, Cappola AR. Subclinical hypothyroidism in older individuals. *Lancet Diabetes Endocrinol* 2022; **10**: 129-141 [PMID: 34953533 DOI: 10.1016/S2213-8587(21)00285-0]

36   **Garber JR**, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woeber KA; American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract* 2012; **18**: 988-1028 [PMID: 23246686 DOI: 10.4158/EP12280.GL]

37   **Pearce SH**, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, Wemeau JL. 2013 ETA Guideline: Management of Subclinical Hypothyroidism. *Eur Thyroid J* 2013; **2**: 215-228 [PMID: 24783053 DOI: 10.1159/000356507]

38   Recommendations | Thyroid disease: assessment and management | Guidance | NICE. Available from: https://www.nice.org.uk/guidance/ng145/chapter/Recommendations#managing-and-monitoring-subclinical-hypothyroidism

39   World Health Organization. Use of glycated haemoglobin (HbA1c) in diagnosis of diabetes mellitus: abbreviated report of

a WHO consultation. World Health Organization Available from: https://apps.who.int/iris/handle/10665/70523

40   **American Diabetes Association Professional Practice Committee**. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; **45**: S17-S38 [PMID: 34964875 DOI: 10.2337/dc22-S002]

41   Home, Resources, diabetes L with, Acknowledgement, FAQs, Contact, Policy P. IDF Diabetes Atlas 2021 | IDF Diabetes Atlas. Available from: https://diabetesatlas.org/atlas/tenth-edition/

42   **McGuire H**, Longson D, Adler A, Farmer A, Lewin I; Guideline Development Group. Management of type 2 diabetes in adults: summary of updated NICE guidance. *BMJ* 2016; **353**: i1575 [PMID: 27052837 DOI: 10.1136/bmj.i1575]

43   **Hostalek U**. Global epidemiology of prediabetes - present and future perspectives. *Clin Diabetes Endocrinol* 2019; **5**: 5 [PMID: 31086677 DOI: 10.1186/s40842-019-0080-0]

44   **Tabák AG**, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. *Lancet* 2012; **379**: 2279-2290 [PMID: 22683128 DOI: 10.1016/S0140-6736(12)60283-9]

45   **Vistisen D**, Kivimäki M, Perreault L, Hulman A, Witte DR, Brunner EJ, Tabák A, Jørgensen ME, Færch K. Reversion from prediabetes to normoglycaemia and risk of cardiovascular disease and mortality: the Whitehall II cohort study. *Diabetologia* 2019; **62**: 1385-1390 [PMID: 31123789 DOI: 10.1007/s00125-019-4895-0]

46   **Cosentino F**, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020; **41**: 255-323 [PMID: 31497854 DOI: 10.1093/eurheartj/ehz486]

47   **Huang Y**, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. *BMJ* 2016; **355**: i5953 [PMID: 27881363 DOI: 10.1136/bmj.i5953]

48   **Echouffo-Tcheugui JB**, Narayan KM, Weisman D, Golden SH, Jaar BG. Association between prediabetes and risk of chronic kidney disease: a systematic review and meta-analysis. *Diabet Med* 2016; **33**: 1615-1624 [PMID: 26997583 DOI: 10.1111/dme.13113]

49   **Bahar A**, Makhlough A, Yousefi A, Kashi Z, Abediankenari S. Correlation between prediabetes conditions and microalbuminuria. *Nephrourol Mon* 2013; **5**: 741-744 [PMID: 23841037 DOI: 10.5812/numonthly.7646]

50   **Dutta D**, Choudhuri S, Mondal SA, Mukherjee S, Chowdhury S. Urinary albumin : creatinine ratio predicts prediabetes progression to diabetes and reversal to normoglycemia: role of associated insulin resistance, inflammatory cytokines and low vitamin D. *J Diabetes* 2014; **6**: 316-322 [PMID: 24251376 DOI: 10.1111/1753-0407.12112]

51   **Živković M**, Tönjes A, Baber R, Wirkner K, Loeffler M, Engel C. Prevalence of moderately increased albuminuria among individuals with normal HbA1c level but impaired glucose tolerance: Results from the LIFE-Adult-Study. *Endocrinol Diabetes Metab* 2018; **1**: e00030 [PMID: 30815561 DOI: 10.1002/edm2.30]

52   **Diabetes Prevention Program Research Group**. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med* 2007; **24**: 137-144 [PMID: 17257275 DOI: 10.1111/j.1464-5491.2007.02043.x]

53   **Wu JS**, Yang YC, Lin TS, Huang YH, Chen JJ, Lu FH, Wu CH, Chang CJ. Epidemiological evidence of altered cardiac autonomic function in subjects with impaired glucose tolerance but not isolated impaired fasting glucose. *J Clin Endocrinol Metab* 2007; **92**: 3885-3889 [PMID: 17666483 DOI: 10.1210/jc.2006-2175]

54   **Knowler WC**, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393-403 [PMID: 11832527 DOI: 10.1056/NEJMoa012512]

55   **Lindström J**, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemiö K, Hämäläinen H, Härkönen P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J; Finnish Diabetes Prevention Study Group. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 2006; **368**: 1673-1679 [PMID: 17098085 DOI: 10.1016/S0140-6736(06)69701-8]

56   **Gong Q**, Zhang P, Wang J, Ma J, An Y, Chen Y, Zhang B, Feng X, Li H, Chen X, Cheng YJ, Gregg EW, Hu Y, Bennett PH, Li G; Da Qing Diabetes Prevention Study Group. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019; **7**: 452-461 [PMID: 31036503 DOI: 10.1016/S2213-8587(19)30093-2]

57   **Jonas DE**, Crotty K, Yun JDY, Middleton JC, Feltner C, Taylor-Phillips S, Barclay C, Dotson A, Baker C, Balio CP, Voisin CE, Harris RP. Screening for Prediabetes and Type 2 Diabetes: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA* 2021; **326**: 744-760 [PMID: 34427595 DOI: 10.1001/jama.2021.10403]

58   **American Diabetes Association Professional Practice Committee**, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, Freeman R, Green J, Huang E, Isaacs D, Kahan S, Leon J, Lyons SK, Peters AL, Prahalad P, Reusch JEB, Young-Hyman D. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. *Diabetes Care* 2022; **45**: S125-S143 [PMID: 34964831 DOI: 10.2337/dc22-S009]

59   **Diabetes Prevention Program Research Group**, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; **374**: 1677-1686 [PMID: 19878986 DOI: 10.1016/S0140-6736(09)61457-4]

60   **Ramachandran A**, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006; **49**: 289-297 [PMID: 16391903 DOI: 10.1007/s00125-005-0097-z]

61   **Shahraz S**, Pittas AG, Kent DM. Prediabetes Risk in Adult Americans According to a Risk Test. *JAMA Intern Med* 2016; **176**: 1861-1863 [PMID: 27695825 DOI: 10.1001/jamainternmed.2016.5919]

62   Adult Positions. ISCD. Available from: https://iscd.org/learn/official-positions/adult-positions/

63   **Camacho PM**, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, Harris ST, Hurley DL, Kelly J, Lewiecki EM,

Pessah-Pollack R, McClung M, Wimalawansa SJ, Watts NB. American association of clinical endocrinologists/american college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract* 2020; **26**: 1-46 [PMID: 32427503 DOI: 10.4158/GL-2020-0524SUPPL]

64 **Salari N**, Ghasemi H, Mohammadi L, Behzadi MH, Rabieenia E, Shohaimi S, Mohammadi M. The global prevalence of osteoporosis in the world: a comprehensive systematic review and meta-analysis. *J Orthop Surg Res* 2021; **16**: 609 [PMID: 34657598 DOI: 10.1186/s13018-021-02772-0]

65 Osteopenia | NEJM. Available from: https://www.nejm.org/doi/full/10.1056/nejmcp070341

66 **Gourlay ML**, Fine JP, Preisser JS, May RC, Li C, Lui LY, Ransohoff DF, Cauley JA, Ensrud KE; Study of Osteoporotic Fractures Research Group. Bone-density testing interval and transition to osteoporosis in older women. *N Engl J Med* 2012; **366**: 225-233 [PMID: 22256806 DOI: 10.1056/NEJMoa1107142]

67 **Hillier TA**, Cauley JA, Rizzo JH, Pedula KL, Ensrud KE, Bauer DC, Lui LY, Vesco KK, Black DM, Donaldson MG, Leblanc ES, Cummings SR. WHO absolute fracture risk models (FRAX): do clinical risk factors improve fracture prediction in older women without osteoporosis? *J Bone Miner Res* 2011; **26**: 1774-1782 [PMID: 21351144 DOI: 10.1002/jbmr.372]

68 **Kanis JA**, Cooper C, Rizzoli R, Reginster JY; Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) and the Committees of Scientific Advisors and National Societies of the International Osteoporosis Foundation (IOF). European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2019; **30**: 3-44 [PMID: 30324412 DOI: 10.1007/s00198-018-4704-5]

69 **Arceo-Mendoza RM**, Camacho PM. Postmenopausal Osteoporosis: Latest Guidelines. *Endocrinol Metab Clin North Am* 2021; **50**: 167-178 [PMID: 34023036 DOI: 10.1016/j.ecl.2021.03.009]

70 Effect of Alendronate on Risk of Fracture in Women With Low Bone Density but Without Vertebral Fractures: Results From the Fracture Intervention Trial | Geriatrics | JAMA | JAMA Network. Available from: https://jamanetwork.com/journals/jama/fullarticle/188299

71 **McCloskey EV**, Beneton M, Charlesworth D, Kayan K, deTakats D, Dey A, Orgee J, Ashford R, Forster M, Cliffe J, Kersh L, Brazier J, Nichol J, Aropuu S, Jalava T, Kanis JA. Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. *J Bone Miner Res* 2007; **22**: 135-141 [PMID: 17042717 DOI: 10.1359/jbmr.061008]

72 **Schousboe JT**, Nyman JA, Kane RL, Ensrud KE. Cost-effectiveness of alendronate therapy for osteopenic postmenopausal women. *Ann Intern Med* 2005; **142**: 734-741 [PMID: 15867405 DOI: 10.7326/0003-4819-142-9-200505030-00008]

73 **Meadows ES**, Klein R, Rousculp MD, Smolen L, Ohsfeldt RL, Johnston JA. Cost-effectiveness of preventative therapies for postmenopausal women with osteopenia. *BMC Womens Health* 2007; **7**: 6 [PMID: 17439652 DOI: 10.1186/1472-6874-7-6]

74 **Eastell R**, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society∗ Clinical Practice Guideline. *J Clin Endocrinol Metab* 2019; **104**: 1595-1622 [PMID: 30907953 DOI: 10.1210/jc.2019-00221]

75 **Bhadada SK**, Chadha M, Sriram U, Pal R, Paul TV, Khadgawat R, Joshi A, Bansal B, Kapoor N, Aggarwal A, Garg MK, Tandon N, Gupta S, Kotwal N, Mahadevan S, Mukhopadhyay S, Mukherjee S, Kukreja SC, Rao SD, Mithal A. The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults. *Arch Osteoporos* 2021; **16**: 102 [PMID: 34176015 DOI: 10.1007/s11657-021-00954-1]

76 Cost of Medicine: Are High-Tech Medical Devices and Treatments Always Worth It? | Hospitals | US News. Available from: https://health.usnews.com/health-news/best-hospitals/articles/2009/07/10/cost-of-medicine-are-high-tech-medical-devices-and-treatments-always-worth-it

77 The Medicalization of Common Conditions | Geriatrics | JAMA Internal Medicine | JAMA Network. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2560372

78 **Grady D**, Redberg RF. Less is more: how less health care can result in better health. *Arch Intern Med* 2010; **170**: 749-750 [PMID: 20458080 DOI: 10.1001/archinternmed.2010.90]