Review Article

Effectiveness and Feasibility of Lifestyle and Low-cost Pharmacologic Interventions in the Prevention of Chronic Diseases: A Review

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Abstract

Chronic diseases are already major causes of morbidity and mortality in Iran, similar to what is seen in other countries. However, there doesn't yet exist a comprehensive plan to cope with the epidemic of chronic diseases in Iran. Several lifestyle and low-cost pharmacological interventions have been proposed to reduce the burden of chronic diseases. Lifestyle interventions require a comprehensive infrastructure that can be quite costly in this country, but several components of extensive lifestyle interventions, including self-help materials and brief advice by health workers, can be integrated into the existing system. Pharmacological interventions may have substantial contribution to the capacity and preparation of Iran's healthcare system to confront the epidemic of chronic diseases. Further research needs to be performed to determine the feasibility and efficacy of each of these methods in order for policy makers to take the appropriate measures on adopting each of these strategies to prevent and control chronic diseases.

Keywords: lifestyle, chronic disease, burden, Iran

Introduction

Chronic non-communicable diseases, such as heart disease, stroke, cancer, diabetes, chronic respiratory diseases, chronic liver disease, and chronic renal disease cause substantial mortality and morbidity worldwide, both in developed and developing countries, including Iran.[1,2]

Whereas until 50 years ago the major causes of death in Iran were infectious diseases, chronic diseases are now clearly the dominant causes of death. Previous studies have shown the rising trend in prevalence of chronic non-communicable diseases in Iran.[3-8] Based on a report by Naghavi et al. in 2003, 58% of total disability-adjusted life years (DALYs) due to all diseases per 100,000 Iranian people have been caused by chronic non-communicable diseases.[2] This major shift in cause of death, from communicable diseases to chronic diseases, is mainly due to Iran's strong primary health-care system that has been very effective in reducing the burden of infectious diseases, infant and under 5-year-old child mortality, maternal mortality, and improving the well-being of mothers and children.[9] However, this system is not designed or well-prepared to manage and reduce the burden of chronic diseases.

It is notable that a major proportion of chronic disease deaths and disabilities (for example 80% of deaths from heart disease and stroke) are caused by a relatively small number of exposures, namely unhealthy diet, lack of exercise, and tobacco smoking,[10] and this provides hope to reduce the burden of these diseases by life-style modification. Specific lifestyle interventions have been designed to address these major risk factors, and there is evidence that integrated and comprehensive preventive lifestyle interventions have stopped and even reversed the rising trend of chronic diseases in a number of countries.[10] However, attempts at reducing chronic diseases via lifestyle interventions have not always succeeded. In fact, there are a large number of studies, which show limited evidence of the benefit from these methods, especially in resource-strained settings in developing countries.[10] On the one hand, without appropriate interventions, one would anticipate that the rates of morbidity and mortality from many chronic diseases could increase; on the other hand, establishment of costly comprehensive lifestyle interventions if not impossible, may not be justifiable in resource-limited countries.[11] Therefore, efficient and inexpensive methods that take advantage of the current strengths and health structure of the country may be highly beneficial.

In the current paper, we summarize the effectiveness of some methods of lifestyle intervention, briefly review Iran's healthcare system and discuss whether appropriate interventions can be integrated in this system without overburdening the system with very expensive interventions.

Lifestyle Interventions

Lifestyle interventions can be classified in different ways, such as passive distribution of information versus active in-

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dividual or group counseling; or primary versus secondary or tertiary prevention.[10] Interventions can also be classified based on targeted high-risk behaviors, such as prevention of unhealthy diet, physical inactivity, smoking, unhealthy sexual behaviors, poor personal sanitation, illicit drug use, and alcohol consumption.[10] The first three (unhealthy diet, physical inactivity, and smoking) account for the major fraction of overall and cause-specific morbidity and mortality of chronic diseases, and are addressed in this paper.

Health outcomes may be those that have direct health consequences (e.g., overall mortality, cancer, or heart failure) or intermediate (surrogate) outcomes (e.g., high blood pressure, blood glucose, or blood lipids); whereas high blood pressure *per se* may not cause mental or physical signs or symptoms, but rather could cause heart failure or stroke. Many studies have examined the relation of life-style interventions with intermediate outcomes.

It is important to understand that although some risk factors such as unhealthy diet have been associated with higher risk of heart disease, interventions to improve diet may or may not be successful for various reasons. Some interventions may not be successful in conveying the right information to the target population because, for example, the message may be beyond the understanding of the target population. Some interventions will fail because they motivate people to change their lifestyle over the short term but not long term. Others, especially pharmacologic ones, could fail because they may have side effects. It is also possible that interventions are too late to have an effect; for example, if people change behaviors at age 50 it may be too late to have a significant effect on their life expectancy.

In the following sections, we summarize our findings on the efficacy of each of these methods and present our view of their practicality and cost-effectiveness.

Dietary advice

Unhealthy diet is a known underlying risk factor of chronic diseases such as cardiovascular disease, stroke, and diabetes.[12,13] High calorie diets could lead to hyperglycemia and diabetes.[14–16] High fat diet is associated with dyslipidemia, including hypercholesterolemia and hypertriglyceridemia, which lead to atherosclerosis, ischemic heart disease, and other cardiovascular diseases.[17,18] Evidence exists that high salt intake can be a risk factor for hypertension,[19] the consequences of which include stroke and chronic renal failure.[19,20] Thus advice for healthy diet has always been an important preventive strategy.

The effectiveness of dietary advice is controversial.[15,19,21,22] In most studies on dietary advice, the effectiveness of advice is examined over the short-term and in well-motivated subjects who adopt intensive diets[23–26]; however, long-term studies show that not only the adherence of subjects declines through time, but also there is a "drop off" in the effectiveness of diet in the long-term.[27] A comprehensive dietary advice, which is more effective when given by dietitians,[28] is costly and practically not feasible in resource-restricted conditions. Brief dietary interventions aimed at the entire population are likely to produce health gain; however, the workload and cost to healthcare systems requires careful assessment.[29]

Many studies have estimated the effects of dietary advice on intermediate risk factors,[30] which include blood lipid levels,[31,32] blood pressure,[33,34] body weight,[35] angiographic measurements,[36] antioxidant intake,[37] and alcohol consumption.[38] The effects on morbidity and mortality, estimated from changes in these intermediate outcomes, assume that the observed changes in dietary habits are sustained and that reductions in risk attributable to these intermediate factors can be combined additively.[29,30]

There are relatively few well-designed long-term studies, which address the reduction of mortality and morbidity of chronic diseases as attributed to dietary advice. The aforementioned scant studies, however, show that dietary advice has little effect on total mortality from cardiovascular events or cancer.[15,19,21,22]

There is some evidence that certain patients respond well to self-help resources. Instead of costly individual dietary advice, the effectiveness of these rather inexpensive resources merits further studies.[29]

Advice for exercise

The association between physical inactivity and sedentary lifestyle with overweight and obesity is established in numerous studies.[39–42] Since the early 1980s, there has been increasing evidence that central fat accumulation has adverse effects on lipids, resulting in elevated triglycerides and very-low-density lipoproteins and low levels of high-density lipoproteins.[43] Moreover, overweight and obesity is associated with type 2 diabetes mellitus.[44,45]

Studies examining the magnitude of weight loss achievable with exercise have shown disappointing results. In a meta-analysis, Garrow and Summerbell concluded that weight lost in exercise programs without caloric restriction is small.[46] In an earlier meta-analysis, Ballor and Keesey also found that weight loss associated with exercise was modest.[47] Failure to lose weight with exercise programs is probably explained by the conversion of fat to muscle. On the other hand, published exercise intervention trials usually have small sample sizes since they are difficult and expensive to conduct, which may be an explanation for the insignificant effect of exercise on weight loss. Moreover, shorter trials tend to produce a slightly more pronounced improvement in glycemic control compared to longer trials. This probably reflects both the higher intensity of the exercise in shorter trials, as well as the difficulties of maintaining compliance with exercise regimes in long-term studies.[48] It is generally difficult to motivate people to exercise. A gradual increase in the intensity of exercise, from

low intensity to moderate exercise performed regularly may be a more successful approach to incorporate exercise into daily lives on a long-term basis rather than introducing more intense levels of exercise at the outset, which will be difficult to maintain over the long term.[49] However, it has been observed in another study that no benefits could be expected in patients who already had poor metabolic control and weak insulin reserves.[50] Above all, motivating people to exercise requires the provision of environmental facilities that can be too costly, especially in resource-restricted settings.

Although evidence supporting the efficacy of exercise to achieve weight loss is disappointing, exercise with or without weight loss improves plasma lipoprotein profiles. There is evidence that exercise increases high density lipoproteins and therefore, may be of particular benefit to people who are abdominally obese, even if no weight is lost by exercising.[51] Exercise as a sole weight loss intervention results in significant reductions in diastolic blood pressure, triglycerides, fasting blood glucose, and insulin resistance.[51] Evidence also shows that high intensity exercise is more effective than lower intensity physical activity, although moderate exercise is no more effective than light exercise.[52–54]

Finally, the same criticism for dietary advice is applicable to advice for exercise: the results of the effect of exercise on intermediate risk factors cannot necessarily be translated into effectiveness in reducing the incidence, mortality, and morbidity of chronic diseases.[51] Due to measurement errors in assessing physical activity, scant well-designed studies have examined the direct effect of exercise on final outcomes.

Advice for smoking cessation

Smoking is the most important risk factor for coronary heart disease and cerebrovascular disease.[55–57] It has been estimated that 40% of heart disease is attributable to smoking compared to approximately 24% for cholesterol and 31% for diastolic blood pressure.[58–61] The causative relationship between smoking and coronary heart disease is extremely well established. Relative risks or odds for smoking and coronary heart disease have been variously estimated to be around 1.5 to 3.[62–64] Smoking also has substantial effect in increasing the risk of cancers of the head and neck, lung, esophagus, stomach, and bladder[65] in addition to the risk of other chronic diseases such as emphysema.[66]

Simple advice by physicians helps people to quit smoking.[67] Even when physicians provide simple brief advice about smoking cessation, the likelihood that someone who smokes will successfully quit and remain a non-smoker 12 months later is increased. Assuming an unassisted quit rate of 2% to 3%, a brief advice intervention can increase cessation by an additional 1 to 3%. Additional components such as group-based counseling, motivational interviewing, or advice for exercise, appear to have only a small effect, though there is a small additional benefit of more intensive interventions compared to very brief interventions. Providing follow-up support after offering advice may slightly increase the cessation rates.[67] Cessation rates are generally higher in trials where nicotine replacement therapy is also used.[68–71] Various features of trials likely to affect absolute quit rates are: the motivation of the recipients who are recruited or treated, the period of follow-up, the way in which abstinence is defined and whether biochemical confirmation of self-reported abstinence is required.[72–74]

The role of healthcare professionals in smoking cessation has been the subject of considerable debate.[75] During the late 1980s there was evidence that advice from motivated physicians to their smoking patients could be effective in facilitating smoking cessation.[76] However, concern has been expressed about the low detection rate of smokers by many physicians and the small proportion of smokers who routinely receive advice from their physicians to quit.[77] Advice on smoking is still not offered systematically. Not all primary care physicians agree that advice should be given at every consultation and some practitioners still choose not to raise smoking cessation as an issue in order to preserve a positive doctor-patient relationship.[78] Still, some research results indicate that satisfaction may be increased by provision of advice.[79]

Some people start smoking again shortly after quitting. Interventions used to help people avoid relapse usually focus on teaching the skills to cope with temptations to smoke. This approach has not been shown to be helpful, either for people who quit on their own or with the help of a cessation treatment, or for those who quit because they are pregnant or hospitalized. There is insufficient evidence to support the use of any specific behavioral intervention for helping smokers who have successfully quit for a short time to avoid relapse. Among drug treatments, extended use of varenicline may help some smokers.[80] Until new positive evidence becomes available, it may be more efficient to focus resources on supporting initial cessation attempts rather than on extended relapse prevention interventions.[81]

Smoking cessation may also have a very substantial role to play in reducing risk among post-myocardial infarction patients. The beneficial impact of quitting smoking after serious heart disease may be as great as or greater than other possible interventions.[82] Quitting smoking is associated with a substantial reduction in risk of all-cause mortality among patients with coronary heart disease.[82] Some studies suggest that risk of a heart attack can decline to that of a life-long non-smoker after quitting,[83–85] while others maintain that there is always some "remnant" risk.[86,87] Some studies have found large reductions in risk no earlier than 2 to 3 years after quitting.[84,85] Moreover, current research suggests that less than half of smokers quit after an acute myocardial infarction, and the most effective ways to help patients with heart disease quit smoking are unclear.[88]

Advice addressing multiple risk factors

In many countries, there is enthusiasm for "Healthy Heart Programs" that use counseling and educational methods to encourage people to reduce their risks for developing heart disease. These interventions may also reduce the risk of other chronic diseases. A review by Ebrahim et al. found that the approach of trying to reduce more than one risk factor or multiple risk factor intervention, as advocated by these programs does result in small reductions in blood pressure, cholesterol, salt intake, and weight loss among others.[89] Contrary to expectations, these lifestyle changes have resulted in little impact on the risk of heart attack or death. Possible explanations are that the small risk factor changes are not maintained over a long-term or are not real because they are reported by studies that are poorly designed and conducted. The availability of foods and better access to recreational and sporting facilities may have a greater impact on dietary and exercise patterns respectively, than health professional advice.[89]

More recent trials examining risk factor changes have cast considerable doubt on the effectiveness of these multiple risk factor interventions[90,91] and even interventions specifically against smoking have prompted a review of the reasons for the frequent failure of such community experiments.[92] A new generation of population-based interventions such as the Minnesota Heart Health Program,[93] Heartbeat Wales,[94] and the Malmö Preventive Project[95] have cast further doubt on the value of such interventions. Meta-analyses suggest that although interventions achieved reductions in risk factors, these were small and did not translate into significant decreases in morbidity or mortality.[96] More intensive interventions might be expected to produce better effects although those used in many of the trials would far exceed what is feasible in routine practice. However, in the Minnesota Heart Health Program, a non-randomized community trial of intensive health promotion, both risk-factor and mortality changes showed virtually no difference between intervention and control communities.[97] The continued enthusiasm for health promotion practices given the failure of these community intervention trials is curious, especially given the huge resources which have been put into them.

It is possible that benefits cannot be detected in the early stages but emerge over time. Long-term follow up of the Multiple Risk Factor Intervention Trial participants has demonstrated increased divergence between control and intervention group mortality rates.[98]

In short, the use of "health promotion" techniques of one-to-one or family orientated information and advice on a range of life-styles (exercise, smoking cessation, and diet) given to people at relatively low risk of cardiovascular disease is not particularly effective in terms of reducing the risk of clinical events. The costs of such interventions are high and it seems likely that these resources and techniques may be better used in people at high risk of cardiovascular disease where evidence of effectiveness is much stronger.[89]

To put it in a nutshell, there is little or no doubt that improving lifestyle, including eating healthier food, exercise, and avoiding tobacco, will improve the primary and secondary outcomes of chronic diseases. Therefore, if high risk behaviors change and intermediate risk factors are controlled, overall and cause-specific mortality and disease incidence will decrease as well. However, the main weakness of lifestyle interventions lies in the fact that they hardly ever can change the high risk behavior in the first place, particularly in the long-term. Overall, lifestyle interventions require a comprehensive strategy to restrict unhealthy behaviors. While the implementation of such a comprehensive strategy requires substantial monetary and human resources, it is worth noting that the lifestyle interventions don't bear fruit in the short-term. Behavioral improvements require propensity and perseverance over long periods of time. High intensity interventions may require trained staff, which should be taken into account in estimating and allocating budget and time.

Pharmacological interventions

The benefits of drug treatments for lowering blood pressure[99–101] and cholesterol[102,103] have been established.[104] However, those people at highest risk of disease benefit most from both hypertension control and cholesterol lowering.[104] Treatment of low-risk populations may result in small treatment benefits being outweighed by small treatment risks which may have occurred in both the Multiple Risk Factor Intervention Trial and the Finnish Businessmen's Trial.[98] There were strong associations between baseline levels of risk factors and net falls observed, suggesting that intervention may be more effective in populations with particularly adverse risk-factor profiles. Evidence from pharmacological trials suggests benefits from reduction of blood pressure and blood cholesterol are observed within two to four years.

One proposed strategy is a fixed dose combination pill (now commonly known as a polypill). Because each component apparently works in addition to the others, net benefits are anticipated to be substantial: risk reduction of more than two thirds within a few years of treatment and prevention of more than 80% of ischemic heart disease events and strokes. Wald and Law suggested the prescription of a polypill for people with known cardiovascular disease and all individuals over age 55 in 2003.[105] The presented strategy was faced with ardent opponents and proponents. Later research, especially the Indian Polycap Study (TIPS) in 2009, supported Wald and Law's estimations,[106,107] yet more research is needed to assess the exact effectiveness of the polypill.[108–111]

Fixed dose combinations are now a core component of care for people with HIV/AIDS, tuberculosis and malaria. As well as improving clinical outcomes, they simplify

distribution of multiple medications, which can be an important advantage in resource-limited healthcare settings. The major challenge remains one of implementation; new strategies are required for the many millions of under-treated individuals with established cardiovascular disease in low and middle income countries. Ideally, these strategies should integrate with systems for other long-term medication delivery, such as those for HIV/AIDS, and complement population-wide measures to address the causes of cardiovascular disease. The components of a polypill are no longer covered by patent restrictions and could be produced at a cost of little more than US$ 1 per patient per month.[10] For people with cardiovascular disease in low and middle income countries, access to preventive care is usually dependent upon their ability to pay, and hence it is this large, underserved group that stands to gain most from a polypill.[105,112]

As the impact of pharmacological interventions is proven by many studies, thus guidelines should be defined for the appropriate provision of medications that are proven in reducing the incidence of chronic diseases, their complications, and their consequential morbidity and mortality. As for the polypill, they may have advantages such as increased efficacy, lower healthcare costs, improved patient compliance and adherence, and improved treatment affordability. However, as mentioned above, their effectiveness and cost-effectiveness remains to be established.

The Iranian healthcare system

Iran's health system is based on the model of public provision of services with subsidies coming through different organizations. At the national level, the Ministry of Health and Medical Education implements the governance, policy-making, planning, financing, and steering of the programs. At the provincial level, the Universities of Medical Sciences and Health Services are responsible for the provision of health services and environmental health. At the township and rural level, a District Health Network, comprised of a district health center, urban and rural health centers, health posts and health houses are charged with this responsibility. Besides the universities of medical sciences, part of the services are provided by insurance companies and the Social Welfare Organization's provincial and district units. The peripheral units (health houses/rural health centers) offer health services free of charge. In other units, the patients avail themselves of the services they need by paying a minimal amount. For services provided by the State Welfare Organization, as characterized by a specific complexity and variation, the costs are calculated on the basis of existing tariffs and paid by the patients. Iran has a very large network of community based health workers (Behrvaz). Iran has completed the epidemiologic transition and the burden of disease indicates that the share of communicable disease is very low.

Iran's health care delivery system can be categorized into three levels, the first two of which are encompassed in the primary health care (PHC) network. The basic PHC level includes: 1) rural health houses with a catchment population of 1,500 staffed by Behvarzes (front line allied health workers); 2) rural health centers containing a physician and other health workers (e.g., nurses, midwives, dental technicians, and environmental health workers) supervising a number of health houses with a population base of 9,000; 3) urban health posts; and 4) urban health centers. The second level of the system is the district health center, which is responsible for the planning, supervision, and support of the PHC network and district hospitals. The third level of the system consists of the provincial and specialty hospitals.

The large network of Behvarz sets a suitable basis upon, which health promotion programs can be founded. The Behvarz can be trained to offer brief advice for quitting unhealthy behaviors at the rural level. Physicians and other health workers can also offer brief or more intensive advice on healthy behaviors in rural areas. Moreover, physicians can provide medications to prevent and treat chronic diseases, mainly ischemic heart disease, diabetes, and stroke at both rural and urban levels as well as throughout the country. Self-help materials can be provided at all levels with minimal cost. However, the establishment and integration of an extensive system to prevent, monitor and treat chronic diseases into the existing health system in Iran requires a comprehensive approach and collaboration of various public and private organizations, which is quite costly and more important, not justified by existing evidence.

Epidemiological, molecular, clinical, community, and behavioral research is essential to generate new knowledge for control of chronic diseases. Translation of this knowledge into effective policies and programmers' for the prevention of chronic disease is also very important.

In order to intensify research in low and middle income countries such as Iran, a necessary first step is to secure partnerships of local experts with experience in conducting research as well as funding and expertise from research organizations in high-income countries. This approach requires a structured, international partnership between local organizations and research institutions with a global perspective. This very important step has already been accomplished in Iran. The Golestan Cohort Study which is the largest prospective study of chronic diseases in the Middle East,[113] with a strong international partnership between local organizations and research institutions with funding and expertise from research organizations in high-income countries is an invaluable platform to study the prevalence and determinants of chronic diseases, and the effectiveness of various interventions for their prevention in Iran. Studies on prevalence of cardiovascular risk factors,[8] and chronic kidney disease[114] have already been performed, as have studies on the effectiveness of pharmacological inter-

ventions for the prevention of cardiovascular diseases.[108–110] Further studies in this regard have been designed and are planned to be launched in the near future. The results of such large scale longitudinal studies can be definitely relied on for proper policy making at the national and international level.

Conclusion

Although lifestyle interventions are proven to overcome certain intermediate risk factors of chronic diseases, their capability to reduce the burden of this group of diseases is under substantial doubt. Comprehensive lifestyle interventions require a strong infrastructure that does not exist in Iran. Thus, certain aspects of these interventions, including self-help interventions and brief advice on the one hand, and pharmacological interventions on the other, can be adopted by Iran's healthcare system. Further research needs to be done to assess the feasibility and efficacy of such life-style and pharmacological interventions in the Iranian health system.

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