Economic growth leads to increase of obesity and associated hepatocellular carcinoma in developing countries

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and the third leading cause of cancer related death worldwide. In recent years, the prevalence of HCC has increased in both developing and developed countries. Most HCC cases develop in the presence of advanced chronic liver disease related to viral hepatitits. In particular hepatitis B virus and hepatitis C virus infections are considered as major HCC risk factors worldwide. However, current studies provide strong evidence for increasing numbers of HCC in nonalcoholic fatty liver disease (NAFLD). NAFLD represents the hepatic manifestation of metabolic syndrome which is based on obesity and insulin resistance. Epidemiologic data clearly demonstrates that NAFLD and obesity-related disorders are significant risk factors for tumor development in general and HCC in particular. As a consequence of life style changes towards higher calorie intake and less exercise, obesity and metabolic syndrome are spreading all over the world. Due to this increase in obesity and metabolic syndrome NAFLD-related HCC will become a major health care problem in the future. In conclusion, better understanding of the impact of NAFLD and obesity in the development of HCC will improve our treatment strategies of HCC and allow preventive measures.

Key words. Nonalcoholic fatty liver disease. Metabolic syndrome. Epidemiology.

INTRODUCTION

Hepatocellular carcinoma (HCC) constitutes approximately 80% of primary liver cancers worldwide. It is the fifth most common cause of cancer in men, the seventh in women (523,000 cases per year, 7.9% of all cancers; 226,000 cases per year, 6.5% of all cancers; respectively) and the third leading cause of cancer death.1 In development of HCC, several etiologic factors play a role. Causes of HCC are hepatitis B virus (HBV), hepatitis C virus (HCV) infections, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD), cryptogenic cirrhosis, aflatoxin B1, and chronic metabolic liver diseases.2 Prevalence and distribution of these risk factors are highly variable and depend on the geographic region and ethnic group.1,3 In recent years, the incidence of HCC has increased in many countries in North and South America, Europe and Asia. Moreover, HCC mortality rates have increased in USA as well as developing countries4 (Figure 1). Turkey, as one example for developing countries, exhibited growing rates of HCC mortality by 21.9% from 2009 to 2013 which is similar to the United States (20%) (Figure 1A). A Mexican study showed that the specific-cause mortality rate of HCC increased by 14% between 2000 and 2006,5 while it remained
The role of NAFLD and obesity in HCC development. 

Mortality rates of malignant liver neoplasm and their correlation with prevalence of obesity in developing and developed countries. 

A-B. Mortality rates from primary liver neoplasm are increasing in Turkey and Brazil over the last years, but slightly decreased in Mexico (which has relatively high rates), and South Africa. These rates are steady in Germany and United States as examples for industrialized countries. Source of data: OECD Health Statistics 2015 Database.
several population-based, epidemiological and clinical studies, conducted in various geographic areas, have clearly demonstrated a significantly increased incidence of HCC in patients with diabetes, NAFLD and obesity, and it is expected that their incidence will continue to increase globally. Therefore, it is crucial to elaborate the role of NAFLD and obesity as risk factors of HCC. This review seeks to summarize the current status, epidemiology, and risk factors of HCC in developing countries. Furthermore it aims to provide an overview of the link between obesity, NAFLD and development of HCC as well as the economic effects of those. Awareness for this severe future health care problem in developing countries must be raised. Here we compared five developing countries, which are Mexico and Brazil (South America), Turkey (Europe-Asia), Lebanon (Middle East-Asia), and South Africa (Africa), to two developed countries, Germany and the United States, to illustrate the differences in economic impact and health care infrastructure.
oped countries, Germany and United States regarding liver malignancy and prevalence of obesity. As an example of developing countries on the verge of industrialization, a particular focus is on Turkey due to its specific socio-economic, educational and industrialized characteristics.

**CAUSES OF INCREASING OBESITY RATES IN DEVELOPING COUNTRIES**

Obesity is defined as excessive fat accumulation (Body Mass Index [BMI] ≥ 30 kg/m²) as a result of excess caloric uptake due to easily available food with high caloric density and overconsumption, and/or insufficient activity and exercise. In recent years prevalence of obesity has increased dramatically worldwide (“obesity pandemic”). This is probably a result of a spreading “western” lifestyle in industrialized countries, which is associated with readily available food with high sugar and fat content, and a more sedentary lifestyle style with less activity and exercise. It is assumed that approximately 3.3 billion adults (57.8%) will become overweight or obese by 2030, if the current trend is maintained.21-22 The prevalence of obesity has increased also in Turkey, with latest WHO verified data (2008) indicating 40.3% of the Turkish population as overweight (BMI 25-29.99 kg/m²) and 16.1% obese (BMI > 30 kg/m²). The follow up to the Turkish Diabetes Epidemiology Study (TURDEP-II) survey showed that the prevalence of obesity had increased from 22.3% to 36%.23 In other studies the mean prevalence of obesity ranged from 19.4% (14.4% in men; 24.6% in women)24 up to 35.1% in a large multicenter nationwide study (15,468 individuals; 14 centers in seven different regions of Turkey; conducted 2000-2002).25 Other large studies found a prevalence of obesity around 30%.26-27 Especially striking are consistently higher percentages for obesity in women in all studies. It has been proposed that this might be a consequence of the particular culture and lifestyle, where outdoor activity and exercise are uncommon for obesity.28 Thus prevalence of obesity among women in Turkey (approximately 35%) is similar to countries with highest rates of obesity in the world such as South Africa, Chile, and Mexico, according to the Cancer Screening and Early Diagnosis Centers (KETEM) study (n = 74,492).29 According to WHO health statistics prevalence of obesity increased dramatically in most countries from 2002 to 2014. In Turkey the prevalence of obesity increased by 17.5%, in Brazil by 9%, in Lebanon by 13.3%, and by 6.8% in South Africa. These rates are similar to those observed in the United States (9.2%) from 2002 to 2014 (Figure 2; Supplementary figure 1). One factor promoting obesity is available or preferred food choice. Especially food with high sugar/carbohydrate and high fat content (high caloric density) may facilitate weight gain. According to the Turkish Ministry of Health, 44.0% of daily energy is sourced through bread only while 58.0% is sourced from bread and other grain derivatives. The consumption of fruit and vegetables is not sufficient and there is a tendency towards higher fast food consumption in urban areas of Turkey. Overall, current nutritional habits in Turkey seem to promote weight gain. In developed countries (i.e. Australia, Canada, USA, England, France), obesity is more common among people with lower socio-economic status and there is a negative correlation between obesity and education.30 In a recent systematic review it has been shown that low prevalence of obesity was recorded in low-income countries (i.e. Bangladesh, India, Vietnam) while high prevalence of obesity was reported in upper-middle-income countries (i.e. Russia, Poland, Seychelles).31 Moreover, a high prevalence of obesity has been shown among individuals with lower socioeconomic status in middle-income countries. Though, high obesity rates shift to lower income groups in high-income countries [gross domestic product (GDP per capita > US $12,275)].27 The reversal hypothesis describes a differential influence of income and education on obesity depending on the GDP.32 A recent study including data from 70 countries, the reversal hypothesis was supported, suggesting that obesity is more prevalent among well-educated individuals in low income countries but becomes more prevalent in uneducated individuals in middle to high income countries.33 In developing countries such as Turkey, Brazil, Lebanon and South Africa, obesity rates among adults show a strong correlation (r² is between 0.8-0.96) with a growing GDP per capita (constant 2011 international $ purchasing power parity; indicator code NY.GDP.PCAP.PP.KD) (Figures 2B-2C; Supplementary figure 2). In Turkey, as example of developing countries, perceived health status is lower in lowest income and low education groups (Supplementary figure 3). This would suggest that Turkey, Brazil, and Lebanon are on the track of many developing countries with increasing GDP and a parallel rise in obesity rates among less educated parts of the population. This emphasizes the importance of information and education regarding nutrient consumption and physical activity for the population in developing countries. Another important factor for development of obesity is physical activity and exercise. There is no representative data on physical activity (during leisure time) in Turkey. One study suggests, that activity and exercise are very uncommon in Turkey, with more than 50% participants stating to perform no physical activities in their spare time.34 Taken together there is a quite large population overweight or obese in Turkey with percentages reaching proportions of the USA. These numbers seem to be continuously growing and the common culture and lifestyle (general food choices, urbanization with
increased consumption of fast food, low physical activity in large parts of the population) in developing countries seem to further promote this problem.

**ECONOMIC CONSEQUENCES OF OBESITY ON HEALTH CARE**

The increasing rate of obesity causes rising health care expenses and accordingly a massive economic burden in USA and UK. Studies in western countries show that the economic cost of obesity increases over time and expenses of the health care system for obesity was already over 2% in France in 1995. In Australia (a country with relatively low prevalence of obesity among industrialized societies), the total annual direct cost of overweight and obesity was $21 billion in 2005. According to the Centers for Disease Control and Prevention, National Public Health Institute of the United States, obese individuals cause 42% more healthcare costs than normal weight individuals. A study from England predicted that about 50-60% of the people by 2050 could be clinically obese and estimated that the prevalence of DM will reach to 31.5% in Turkey by the year 2025. Another projection model projected that the prevalence of DM will reach to 31.5% in Turkey by the year 2025. Another projection model reached a similar proportion with a predicted prevalence of DM of at least 28.3% by 2030.

In the last decade all components of metabolic syndrome have increased dramatically all over the world. Thus, there is an overall trend of uncontrollable increase in the prevalence of metabolic syndrome. In the USA the prevalence of MetS increased from 32.9% in 2003-2004 to 34.7% in 2011-2012. In the Turkish adult population, according to Adult Treatment Panel III criteria, the overall prevalence of MetS was estimated to be near 28.8% in the Mediterranean region of Turkey and 26.9% in the Northern region. However, it reached up to 43.2% among elderly subjects in the same regions and up to 61.7% in the central part of Turkey.

There is a clear connection between insulin resistance and NAFLD. Generally, hyperinsulinemia is a frequent feature of chronic liver diseases regardless of etiology. Moreover, higher levels of serum insulin are a significant risk factor for HCC progression not only in NAFLD, but also in chronic viral and alcoholic hepatitis patients. Besides HCC, hyperinsulinemia was attributed as risk factor for solid organ tumors in non-diabetic subjects.

Taken together prevalence of insulin resistance and MetS in Turkey is as high as in industrialized countries, similar to the rates of overweight and obesity. Furthermore, there is a trend of continuing increase of this risk factor for multiple co-morbidities and elevated mortality in Turkey.

**PREVALENCE OF INSULIN RESISTANCE, DIABETES AND METABOLIC SYNDROME IN TURKEY AS AN EXAMPLE OF DEVELOPING COUNTRIES**

Following the obesity pandemic the prevalence of insulin resistance has increased globally in the recent years. In US, it is estimated that the prevalence of pre-diabetic patients has risen from 29% in 2000 to 38.5% in 2012. According to the TURDEP II study the prevalence of pre-diabetic patients increased by 106% from 2002 to 2013 and reached 30.8% in Turkey.

**PREVALENCE OF NONALCOHOLIC FATTY LIVER DISEASE IN DEVELOPING COUNTRIES**

As described above NAFLD represents the liver manifestation of the metabolic syndrome and is closely associated to obesity and T2DM. Progression of NAFLD to NASH, cirrhosis, and HCC causes liver-related morbidity and mortality. In parallel to the worldwide obesity pandemic, NAFLD rates are increasing in industrialized countries and those adopting the “western” lifestyle. Prevalence of NAFLD is ranging from 20% to 50% depending on definition criteria and diagnostic methods used in most studies. It is estimated that prevalence of NAFLD is between 10-46% in the USA, 15-40% in European countries, and 9-40% in the Asian population. Prevalence rates of NAFLD are higher with increasing BMI and can reach proportions of 50-80% in obese. Approximately 90% of patients with NAFLD have at least one feature of MetS and NAFLD may be involved in the pathogenesis of insulin resistance.
and MetS. In developing countries, there are limited data regarding the prevalence of NAFLD. It seems that awareness for the risks of obesity and NAFLD are not very high in those countries, as the focus in liver disease pathologies is still mostly on viral hepatitides. Nevertheless, based on the above discussed numbers of obesity and diabetes in populations of developing countries, it is highly probable that a significant number of individuals have undiagnosed NAFLD. Studies in other populations have shown that roughly two thirds of diabetic patients may have NAFLD. Prevalence of NAFLD is increasing not only in adults but also in obese children and varies between 2.6% and 9.6% associated with sex, age, and ethnicity of children. In several studies among children, prevalence of NAFLD ranged between 13% and 80% and was correlated to obesity rates. In another study MetS, defined according to modified WHO criteria adapted for children, was found in 27.2% of young people, with a significantly higher rate among obese adolescents aged 12-18 years (37.6%) than among obese children aged 7-11 years (20%). Furthermore, in one study from Turkey prevalence of MetS in obese children with NAFLD was significantly higher than in those without liver disorders (54.8% vs. 14.9%, respectively). Despite a lack of current data on NAFLD in developing countries, obesity and diabetes rates suggest a significant proportion of individuals may be affected, which will further increase due to growing numbers of child and adolescent obesity.

**NAFLD as a Growing Cause of HCC**

In recent years, especially in developed and many industrialized countries, NAFLD is considered the most common underlying HCC risk factor (59%) followed by diabetes (36%) and HCV infection (22%). NAFLD has been described as the sole growing chronic liver disease in the USA, while all other chronic liver diseases remained at a stable proportion. In a German single center study, the proportion of NASH-associated HCC was 24% and NASH represented the leading cause of HCC in this study. Since then a growing body of evidence has demonstrated that NAFLD is an important risk factor for HCC development and that HCC may occur in NAFLD even without cirrhotic alterations. On a global scale the decrease of HCV prevalence with a parallel increase of obesity and subsequently NAFLD will lead to a shift toward higher rates of NAFLD-associated HCC. While this has been recognized by most industrialized countries, in many developing countries or those with currently still high HCV rates, this gradual shift seems to go largely unnoticed.

**OBESITY AND NAFLD AS UNDERLYING CAUSE OF HCC**

As described above a global rise of NAFLD following the obesity epidemic is expected and already visible in industrialized countries. In consequence of this development HCC-incidence due to NAFLD will increase with a delay of a few years. By now a significantly increased incidence of HCC in obese patients has been documented in various regions. In a cohort of 900,000 American adults, the risk of dying from liver cancer was 4.5 times higher in obese men compared to a control group. Epidemiologic data demonstrates a parallel rise in prevalence of obesity, NAFLD, and HCC. A meta-analysis from Europe, the USA, and Asia showed that relative risks to develop HCC were 1.17 for overweight and 1.89 for obese individuals. Diabetes increases risk of HCC three-fold, according to an American-population-based study. NAFLD, which is present in up to 90% of all obese persons and up to 70% of T2DM patients, appears to play a key role in HCC development. In Mexico a parallel increase of liver cancer mortality and obesity in the population have been described, confirming associations of metabolic syndrome and HCC. Unfortunately in most studies on HCC from other developing countries, NAFLD and NASH as cause for liver tumors are neglected, while still high rates of HCV and HBV associated HCC are presented. Most studies performed in developing countries do not discuss NAFLD in the setting of HCC. In parallel 5-25% of HCC cases remain as cryptogenic or “idiopathic”. In one study from Turkey the proportion of NASH-associated HCC was given as 3.5% in 2010. Compared to the proportion of the population overweight or diabetic in developing countries, especially in Turkey, this ratio seems rather low. There are several factors that may complicate this issue and could lead to erroneous numbers. The main risk factors for HCC recognized in developing countries still are viral hepatitides. Once a viral cause has been established as diagnosis, other risk factors as obesity or diabetes are not tested for (at least they are not presented in the described studies). In addition many “idiopathic cases” can be found in the studies on HCC, while it has long been established that NAFLD may be the real cause of cryptogenic HCC. Finally NAFLD or even obesity alone may aggravate any chronic liver disease (including viral hepatitides) and could thus further promote tumor development in HCV or HBV. This might be the case in Turkey and other developing countries, although no data is available on metabolic risk factors in common descriptions of HCC cohorts.

Currently data on NAFLD-associated HCC is extremely scarce in developing countries. Awareness for NAFLD in obese and/or diabetic patients and associated
risks for the liver has to be increased in clinicians in these regions. Moreover the serious health risks of NAFLD, including development of HCC from non-cirrhotic livers, should be considered.

CONCLUSIONS

NAFLD is the most common cause for chronic liver disease in developed countries which is closely associated with obesity. In developing countries obesity rates are similar to those in the USA, though prevalence of NAFLD is presented as low or widely unknown. Increasing prevalence of NAFLD-associated HCC globally results from improved prevention of HCV/HBV infections in developing countries on the one hand and rising numbers of NAFLD following the obesity pandemic. Higher income and a change of life style towards “western” habits may further aggravate the obesity problem in developing countries. Prevention of obesity and NAFLD remain the best long-term strategy to avoid serious health care problems in the near future. Turkey is in a unique situation among developing countries on the verge of industrialization and there is already a large proportion of the population overweight or obese. Obesity associated co-morbidities of the liver seem to be far less common than in other industrialized nations. Quick action to counter the trend of continuing weight gain and spread of the obesity epidemic might safe developing countries from a massive health care problem. As no treatment for NAFLD is available, yet, an effort should be made to expand general education on a healthy life style to avert a drastic increase of NAFLD-related morbidity, in particular from HCC.

ABBREVIATIONS

- BMI: body mass index.
- HBV: hepatitis B virus.
- HCC: hepatocellular carcinoma.
- HCV: hepatitis C virus.
- KETEM: Turkey Cancer Screening and Early Diagnosis Centers.
- MetS: metabolic syndrome.
- NAFLD: nonalcoholic fatty liver disease.
- NASH: nonalcoholic steatohepatitis.
- T2DM: type 2 diabetes mellitus.
- WHO: World Health Organization.

CONFLICT OF INTEREST

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Supplementary figure 2. Gross domestic product of selected developing countries over the last decade. Gross domestic product (GDP) per capita in all examples of developing countries has increased over the last decade. GDP per capita (constant 2011 international $, PPP, indicator code: NY.GDP.PCAP.PP.KD), World Bank.
Supplementary figure 3. Perceived health status by socio-economic status in Turkey. Data refers to percentage of the population in good/very good health. Source of data: OECD Health Statistics 2015 Database.