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CHANGING TRENDS IN AETIOLOGY OF LIVER DISEASES IN IMMIGRANTS IN SOUTHERN ITALY: FATTY LIVER, AN OBSERVATIONAL RETROSPECTIVE STUDY

Community Medicine

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KEYWORDS

Fatty liver; Liver Diseases, Alcoholic; Non-alcoholic Fatty Liver Disease; Immigrants

The rate of migration in Italy is constantly growing with immigrants making up about 8.7% of the country's population and 4.8% in our district (Foggia-Puglia, Southern Italy) (1). These are people who are both already resident in Italy for one or more generations, and new arrivals. Migrants in our geographical area mainly come from Eastern Europe, Sub-Saharan Africa, Middle-East and South Asia. Such a high number of immigrants result in a minor change in the epidemiological pattern of diseases with an increase in certain infections, which are imported or contracted in our country such as HIV, TB and viral hepatitis (2), but can also include cancers, cardio-cerebrovascular and autoimmune diseases (3-4). Other major health concerns mainly include metabolic syndrome (5), as well as problems related to social discomfort such as alcoholism (6). The incidences of hyperlipidaemia, obesity and diabetes mellitus amongst immigrants, has increased significantly over the years due to social and economic progression, and lifestyle changes, which in some cases are due to high-fat and high-sugar diets and a lack of physical exercise (5-7). One of the most common clinical problems is fatty liver (FL): a metabolic disorder characterized by an excessive accumulation of triglycerides in hepatocytes that can be induced by multiple causes. Chronic alcohol intake is certainly one of the main causes (ALD), while another important reason is NAFLD (Non-Alcoholic Fatty Liver Disease), which represents the hepatic component of metabolic syndrome (8). FL has now become a major cause of liver related morbidity and mortality, with an incidence of around 20-25% worldwide. It is present mainly in native populations of developed countries, but its prevalence is also increasing amongst immigrants (8-10).

In recent years, we observed stable incidences of viral hepatitis amongst immigrants who were screened, combined with a significant simultaneous increase of ALD, (making up approximately 13% of liver disease), and about 3% of NAFLD. However, genetic and ethnic factors also seem to come into play causes favouring the onset of FL (10). We conducted a retrospective study to assess the prevalence of FL, in a cohort of our screened immigrants, comparing various parameters, specific to the ALD and NAFLD, between diseased and healthy individuals. In addition, we evaluated their clinical effects in relation to race and ethnicity, and different socio-economic issues and sanitation.

Patients and methods

Data of 395 immigrants records, did not present any other hepatic disease and/or HIV infection have been analysed in this observational retrospective study to evaluate the prevalence of FL, and reworked according to the hypothesized research project. The patients attended at our ambulatory between April 2009/December 2016; they had been followed by us, continuously, each for at least 18 months; the reworking, for each patient under examination, concerned data of 8-12 months. Immigrants originated from several ethnic groups and had different demographic characteristics (regular/irregular subjects, living with family/in ethnic community/in refugee camps, of different religions etc.). To obtain baseline demographic, clinical, and socioeconomic information, and to assess their previous exposure to liver diseases, we examined medical records. These records were either completed when subjects made first contact with, and/or had subsequent checks by, the healthcare facility to which they referred. Informed consent was not requested because this study included only data gathered in an anonymous form from the hospital discharge charts. Furthermore, given that the study was retrospective and descriptive, it was not submitted to the Ethics Committee of our hospital. All procedures followed, were in accordance with the ethical standards of for human observational studies and with the Helsinki Declaration of 1975, amended in October 2013.

To diagnose ALD/NAFLD, we analysed and cross-referenced general health history data, particularly the use/abuse of alcohol, and results of biochemical, serological, virological, ultrasonographic and medical examinations. Only a fraction of subjects agreed to undergo liver biopsy.

We ascertained whether subjects consumed alcohol previously or began consuming after coming to Italy, and the quantity of daily consumption: moderate/standard when equivalent to no more than 2-3 alcohol units (36 grams) for men, 1-2 units (24 grams) for women and 1 unit (12 grams) for the elderly. Drinking habits associated with an increased risk of alcohol-related liver disease are defined as consuming 15 or more units per week.

For metabolic syndrome, we analysed Body Mass Index (BMI: weight, kg/height/m^2), waist to hip ratio (WHR), triglyceride, cholesterol, sugar and insulin levels. Fasting sugar >126 mg/dl was considered impaired glucose metabolism. Insulin sensitivity was estimated using the homeostasis model assessment (HOMA) method; triglyceride level >150 mg/dl and cholesterol level >200 mg/dl were defined as abnormal.

All enrolled patients underwent abdominal ultrasound, the degree of steatosis was graded from 1 to 3, depending on the percentage of cells with lipid droplets (grade 1: mild 0-33%, grade 2 moderate: 34-66%, grade 3 severe: 67-100%).

STATISTICALANALYSIS

Categorical data are presented as absolute numbers and proportions, and continuous variables are expressed as medians and ranges.

The chi-square test was used to compare categorical variables (geographical area of origin and HBV markers). Continuous variables (sex, age, living conditions, habits and risk factors and ALT levels) were compared by Student's t-test for independent samples. To assess the difference in severity of liver disease between ALD and NAFLD subjects, the level of steatosis was analysed using 2x2 tables, $\chi 2$ test. p values <0.05 were considered as significant.

RESULTS

The mean age of the 395 patients was 29.8±7.5 (range: 19–67years), of which 221 (55.9%) were males. The majority (197, 49.9%) were Africans (mainly from the Horn of Africa); 132 (33.4%) came from Eastern Europe (mainly from Romania and Albania), 51 (12.9%) were Asians (mainly from India, Pakistan, Bangladesh and China) and 15 (3.8%) were from the Middle East. A clear majority (252/395; 63.8%) were irregular immigrants, and largely (228/395; 57.7%) socially un-integrated subjects. Less than half of them lived with their families (165/395; 41.7%), while others were divided between reception centres and ethnic communities. Only a modest percentage of subjects (137/395; 34.6%) had stable work. The average length of living in Italy was 7 years (range: 9 days-18.3 years).

Just over half of the immigrants reported alcohol intake (202/395, 51.1%). These were mainly Eastern Europeans and Africans, while a rather high proportion of Asians and Middle Easterners (mainly

Muslims) claimed to be abstainers (p>0.05). In a substantial proportion of cases, about 59.8%, alcohol was already being consumed prior to coming to Italy. Two hundred sixty-six (67.3%) subjects were healthy, while 129/395(32.6%) subjects, 58.1% males, were affected by FL (tab. 1).

Fatty liver

FL presented overlapping percentage values amongst Africans (60/129, 46.5%) and Eastern Europeans (52/129, 40.3%) (p>0.05), but significant differences were observed when comparing these groups to Asians (14/129, 10.8%) and Middle Eastern immigrants (3/129, 2.3%) (p<0.03) (tab. 1).

The majority of subjects with FL (73/129, 56.6%) consumed alcohol. Consumption was reported to be generally low (1-2 units/day) in 31/73 (42.5%) patients; however, accurate medical history showed that 42/73 (57.5%) patients (both men and women) with ALD, on average, consumed about 3 units or more/day.

NAFLD, often related to metabolic syndrome, was the cause of FL in 56/129 (43.4%) patients. Although a proportion of this group reported consumption of minimal amounts of alcohol (<1 unit/day), the majority did not drink.

The mean age of subjects who presented with FL was 32.3 years in NAFLD patients, and 35.2 years for those with ALD. Amongst the 73 ALD subjects no significant differences were found between immigrants who had been resident for longer in Italy and new arrivals (38vs.35, p>0.05); while a significant difference was seen amongst NAFLD patients between the two groups: 43 were already resident for several years and 13 were newly arrived subjects (p<0.01).

Following univariate analysis, no significant differences were found for age and sex between healthy individuals and FL patients, as well as between the two groups with steatosis (p>0.05). The living environment (reception centres, ethnic community and family), so as irregular condition, social integration levels and occupational status as a predisposing factor for social purposes, had no significant impact on FL; nor did these factors have a significant importance to differentiate patients with FL from the controls. (p>0.05) (TAB.2).

ALD/NAFLD and risk factors

Africans had significantly higher blood pressure (both diastolic and systolic), lower plasma triglyceride levels and higher cholesterol levels than other ethnicities (p<0.001). The associated prevalence of severe obesity (BMI>30 kg/m^2), diabetes and insulin resistance was consistent across the Asian, Middle Eastern and African groups, while it was significantly lower in Eastern Europeans (p<0.001). Although not significant, BMI was found to be lower in all women, particularly amongst Eastern Europeans, compared to women from other ethnicities (p> 0.05).

The WHR of male patients with FL (0.93 ± 0.05) was markedly higher than healthy individuals (0.87 ± 0.06) (P<0.01), while the WHR of female patients was comparable between the three groups (healthy subjects, ALD and NAFLD) (p>0.05) (Tab 2). Furthermore, significant differences were noted for these parameters between ALD and NAFLD subjects (p<0.003). Amongst drinkers, the reported history of alcohol abuse before coming in Italy increased the risk of developing the disease (p<0.05). There was also a significant association between the clinical evolution of FL and drinking more than 3 alcohol units per day(p<0.001). Eastern European immigrants were more likely to develop liver disease of alcoholic origin (p<0.05).

Serum biochemical parameters

Individuals with FL, expressed as mean ± standard deviation (median) vs. controls presented ALT 0.8±0.2×ULN vs. 0.5±0.6×ULN, (p>0.05), prothrombin activity 82.8%±15.1vs.66.6±15.1%; p<0.01). The lipid profile results (median) were total cholesterol (183.2±41.04 vs.161.8±35.9 mg/dL, respectively; p=0.02), and triglycerides 91.1±45.2 vs. 84.6± 37.9 mg/dL(p>0.05). The fasting glucose was 92.6±13.8 g/dL, fasting insulin 7.1±4.7 µIU/mL, glycated haemoglobin 6.0%±1.3%. and albumin 3.7±0.4 g/dL, weighted overlapping values (p<0.03). GGT and AST were markedly higher in patients with FL than in subjects without steatosis (P<0.01) (tab. 1-2).

Ultrasound staging

Amongst the 129 patients with biochemical criteria of FL, echo-tomography detected the following: 13 subjects (10.1%) showed minimal signs of steatosis in patches; 11 (8.5%) individuals (5 ALD and 6 NAFLD) had FL grade 1; 71 (55.1%) had FL grade 2 (37 ALD and 34 NAFLD); 29 (22.4%) had FL grade 3 (14 ALD and 15 NAFLD); 5 (3.9%) showed signs of hepatic cirrhosis (3 ALD, 2 NAFLD). No individual showed ultrasound signs of HCC. No significant differences were seen in the degree of steatosis (p>0.05) between ALD and NAFLD subjects. The patients with more advanced hepatic steatosis had significantly higher BMI (26.89 ± 2.78 kg/m2) compared to those with milder steatosis (21.17 ± 2.96 kg/m2) (P<0.01). Amongst the 18 patients with FL, grade 3 and cirrhosis, 8 were females (tab. 3).

Fifty four/129 (27 ALD, 27 NAFLD) individuals agreed to undergo liver biopsy (27 Eastern Europeans, 13 Africans, 11 Asians and 3 Middle Easterners). Histologic steatosis was detected in 49 (66.2%) patients with no significant differences seen for degree and percentage difference between the various ethnic groups (p>0.05). Three patients, of which two were women who were both affected by ALD, showed a histologic picture of cirrhosis.

DISCUSSION

Currently one of the most common worldwide liver diseases is FL. The main factors responsible for it are: NAFLD, which is often related to metabolic syndrome and ALD linked to harmful alcohol abuse (9). It is difficult to quantify, considering the different aetiologies, the number of people affected by FL. It is, however, a pathology typical of both well-being and social distress, and is transversal, affecting both the wealthiest and the poorest classes; immigrants can be included in both social classes.

The worldwide prevalence of NAFLD is estimated to be around 25%. It is most prevalent in the Middle East (31.8%), followed by South America (30.4%). NAFLD was found to be least prevalent in Africa (13.5%) . Comparatively, the prevalence of NAFLD in Asia, Europe, and North America was found to be 27.4%, 23.7%, and 24.1% respectively (11). Although there are several studies that have delved further into metabolic associations of NAFLD in different races and ethnicities, only a few studies have assessed its prevalence in immigrant populations. In Italy, NAFLD prevalence was estimated at 20% of the resident population including both natives and immigrants (12-13).

Another extremely important factor of steatosis is increasing levels of alcohol consumption (ALD). An estimated 43% of the world population are current drinkers. Alcohol is consumed by more than half of the population in three WHO regions – the Americas, Europe (in Italy 22.2% of resident population including both natives and immigrants (6)) and the Western Pacific (14-15). Amongst our immigrants, steatosis was present in more than a third of subjects, mainly as ALD (73/129 pts.) rather than NAFLD (56/129 pts.), without there being a significant prevalence of one aetiology over another. ALD was more prevalent amongst Eastern Europeans (39.7%) mostly Belarusians, Czechs and Lithuanians (14), and Africans (35.6%) when compared with other ethnic groups. Africans (48.2%) exhibited the greatest prevalence of NAFLD, followed by Eastern Europeans (41.0%).

Age and sex, as well as regular/irregular condition, social integration level and occupational status did not seem to have an impact on diversifying patients; the exception were Africans who were 3-6 years younger compared other ethnicities.

ALD

It is difficult to precisely estimate the amount of alcohol consumed by immigrants, epidemiological data shows a constantly evolving phenomenon, in fact seems to be a trend towards an increase to consume alcoholic beverages in traditionally teetotal groups, like younger subjects, Muslims or Hindus (16-17). Alcohol consumption has different connotations depending on the countries, cultures, and religions of origin, making it difficult to fully understand the phenomenon. The abuse is often overlooked, due to a lack of adequate means and methods of investigation. However, recent studies assume that 25% of immigrants in Italy consume alcohol (18).

The most striking findings of our ALD subjects are a male

preponderance (71.2%), an older mean age of women (52.9 years), an increase with age in both sexes and a high proportion of subjects with a history of alcohol abuse before coming in Italy (mainly Eastern European subjects). Some studies, including ours, have highlighted alcoholic liver disease in men (19). This could be due to the fact that men generally drink more frequently than women and, more often, are heavy drinkers or even alcoholics. This is regardless of their origin or geography (19, 20). The average age of our male subjects with ALD (mainly African and Middle Eastern) was rather young, suggesting an early addiction to alcohol, and to episodes of 'binge drinking'. This pattern of drinking usually corresponds to 5 or more drinks on a single occasion for men or 4 or more drinks on a single occasion for women, generally within about 2 hours (21).

Although the number of women suffering from ALD is less than men, they are more vulnerable to alcohol-induced liver disease, alcoholic hepatitis, and liver cirrhosis even when drinking the same amount of alcohol as men. Their greater vulnerability and lower levels of safety with respect to alcohol consumption have long been recognized, regardless of their ethnicity (in our study a relatively high percentage of women had severe hepatitis or cirrhosis) (22). Some factors may explain this difference: less gastric alcohol dehydrogenase production and less alcohol distribution volume in women. Moreover, female hormones are believed to increase alcohol-mediated liver injury in an unknown manner (23). This could explain the greater progression of the disease in women, with a more rapid increase in liver fibrosis in late menopause compared to other stages in a woman's life (reproductive/premenopausal/early menopause) (24).

NAFLD

Different ethnic groups of our study displayed multiple differences in NAFLD, Africans and Eastern Europeans had the greatest prevalence while, interestingly, Asians and Middle-Easterners had the lowest prevalence of NAFLD despite having the highest prevalence of obesity and metabolic syndrome (11).

NAFLD was more prevalent in men than in women (58.1% vs 41.9%), mainly among Eastern Europeans. This finding can be explained by the higher waist-to-hip ratio (WHR) in men. WHR correlates with visceral adipose tissue (VAT) and increased lipid content in the liver. It also independently links hypo-adiponectinaemia, hypertrophic obesity and increased visceral adiposity with peripheral and hepatic insulin resistance (25). NAFLD development requires two steps: at first simple steatosis and subsequently a source of oxidative stress capable of initiating significant lipid peroxidation (26). Dietary habits may promote NAFLD either directly by modulating hepatic triglyceride accumulation and antioxidant metabolism, or indirectly by affecting insulin sensitivity and postprandial triglyceride metabolism (27). Different racial and ethnic groups have substantial differences in their diet. This can obviously have a different effect on the propensity to develop FL, as we have observed in our subjects. Interestingly, we found a graded relationship between acculturation and dietary measures, where more acculturated immigrants (subjects resident for longer in Italy), regardless of their ethnicity, generally had a more adequate and richer diets. Eastern Europeans reported higher energy and carbohydrate intakes and a lower percentage of energy from fat with lower levels of cholesterol than the other groups (mainly Asians) and Africans had a higher intake of sweets.

Our; African population with NAFLD is younger than the other ethnicities; this may reflect an earlier onset of disturbed fat metabolism contributing to insulin resistance and an earlier diabetes onset, which is also due to the diet.

Only a proportion of patients, with suspected FL, agreed to undergo biopsy, while in the others steatosis was mainly diagnosed by imaging and/or using biochemical criteria. Liver biopsy is currently the optimal examination for the diagnosis and staging of liver steatosis, but invasiveness and cost preclude its use as a screening tool in general populations. However, histological analysis of our patients, has almost completely confirmed the ultrasound diagnosis, confirming the validity of the latter as an elective examination for FL (28).

CONCLUSIONS

FL is quite frequent in immigrants and the problem is likely still underestimated; it does not seem directly related to the ethnicity, living environment, regular/irregular condition and employment status. Instead, changes in lifestyle and diet (exaggerated or incongruous) are of considerable importance. The growing phenomenon of alcoholism is certainly the main factor in the genesis of liver steatosis amongst migrants.

Main points

1. FL in immigrants is underestimated but frequent and with a growing trend.
2. Changes in lifestyle and diet are of considerable importance and linked to habits like insufficient mobility.
3. Alcoholism is a growing phenomenon among risk categhories.
4. Genetic factors related to ethnic groups may ease the insurgence of hepatic steatosis.

Tables

Table 1. Demographic characteristics, living conditions, habits and risk factors of the 395 enrolled subjects

	Fatty liver patients N.=129		Controls N.=266	
Age				
Mean – SD (yrs)	30.1 – 7.5		29.4 – 7.5	
	N.	%	N.	%
Sex				
Male	75	*58.1*	139	*52.3*
Geographic area of origin				
East Europe	52	*40.3*	77	*35.4*
Africa	60	*46.5*	140	*46.9*
Asia	14	*10.8*	35	*15.6*
Middle East	3	*2.3*	14	*2.1*
Irregular immigrant				
Yes	76	*58.9*	177	*66.7*
Social integration level				
Not integrated	71	*55.0*	158	*58.3*
Living environmental				
Asylum centre	40	*31.0*	107	*33.3*
Community of immigrants	30	*23.3*	56	*24.0*
Family	59	*45.7*	103	*42.7*
Occupational				
None/Uncertain	80	*62.0*	177	*64.6*
Alcohol intake				
Yes	73	*56.6*	124	*59.4*
Before they come to Italy	62	*37.2*	62	*29.2*
N. of alcohol unit				
1	9	*12.3*	46	*35.1*
2	22	*30.1*	56	*45.6*
3	19	*26.0*	8	*7.0*
>3	23	*31.5*	14	*12.3*

SD: statistical deviation

Table 2. Main clinical characteristics and risk factors of individuals (N° and %) with FL (ALD, NAFLD), and controls.

Total patients	ALD: 73 (%)	NAFLD: 56 (%)	Controls: 266(%)
BMI <18.5 Kg/m^2 under weight	8 (10.9)	3 (5.3)	25 (9.3)
BMI<24.9 Kg/m^2 normal weight	34 (46.6)	21 (37.5)	181 (68.0)
BMI<29.9 Kg/m^2 moderately obese	28 (38.3)	20 (35.7)	33 (12.5)
BMI≥30.0 Kg/m^2 severe obese	3 (4.2)	12 (21.5)	27 (10.2)
WHR (mean cm)	91	95	87
Type 2 Diabetes	13 (17.8)	27 (58.2)	59 (22.2)
HOMA >2.5	11 (15.0)	21 (37.5)	36 (13.5)
Alcohol:unit ≤1/d	9 (12.3)	5 (8.9)^	46 (37.1)
Alcohol: unit 2/d	22 (30.1)	11 (19.6)^	58 (45.2)
Alcohol:unit 3/d	19 (26.1)	/	8 (6.4)
Alcohol:un. >3/d	23 (31.5)	/	14 (11.3)
Fatty Liver gr. 1	7 (9.6)	6 (10.7)	21 (7.9)
Fatty Liver gr. 2	45 (61.6)	33 (58.9)	/
Fatty Liver gr. 3	21 (28.8)	17 (30.4)	/

These patients were not classified as alcohol abusers
BMI: Body mass index
WHR: wise-to-hip ratio
HOMA: Homeostasis model assessment

Table 3. Main clinical characteristics and risk factors of individuals (N° and %), with and without Fatty Liver, by ethnicity.

	Africans 200	Asians 49	East-Eur.129	Mid-Eas 17
BMI<18.5Kg/m^2	63 (31.5)	14 (28.6)	42 (32.5)	5 (29.4)
BMI<24.9Kg/m^2	68 (34.0)	13 (26.5)	46 (35.6)	5 (29.4)
BMI<29.9Kg/m^2	42 (21.0)	7 (14.3)	25 (19.5)	3 (17.7)

BMI≥30.0Kg/m^2	27 (13.5)	15 (30.6)	16 (12.4)	4 (23.5)
WHR(mean cm)	83	98	88	96
Type2Diabetes	87 (35.5)	32 (43.8)	27 (16.5)	1
HOMA >2.5	79 (32.2)	31 (42.4)	21 (12.8)	1
Alcohol:unit1/d	21 (10.5)	8 (16.3)	18 (13.9)	8 (47.0)
Alcohol:unit2/d	12 (6.0)	25 (51.0)	36 (27.9)	5 (29.4)
Alcohol:unit3/d	6 (3.0)	9 (18.4)	11 (8.5)	1 (5.8)
Alcohol:un.>3/d	3 (1.5)	15 (30.6)	19 (14.7)	/
Fatty Liver	60 (30.0)	14 (28.6)	52 (40.39	3 (17.6)
FL grade 1	32	4	19	2
FL grade 2	20	5	21	1
FL grade 3	8	5	12	/

Patients with FL, compared to the controls, exhibited a higher, but not significant, mean total cholesterol (183.2±41.0 4vs.161.8±35.9 mg/dL, respectively; p=0.02), greater prothrombin activity (82.8%± 15.1vs. 66.6±15.1%; p<0.01), a moderately higher median fasting insulin (7.1±4.7 μIU/mL vs.3.3, p=0.04). There was no significant difference in ALT between the different groups of subjects (p>0.05) (0.8±0.2 vs.0.5±0.6 ×ULN, respectively).

BMI: Body mass index
WHR: wise-to-hip ratio
HOMA: Homeostasis model assessment
FL: fatty liver

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