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Usefulness of FRAX® in the study of fractures in the alcoholic patient

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Summary

FRAX® index is a prognostic tool to assess the risk of osteoporotic fracture. Although ethanol ingestion, liver disease and body mass index are considered independent prognostic factors in the FRAX® score, we have observed that in chronic alcoholics there are several variables not included in the FRAX® index, which show a relation with prevalent fractures and/or low BMD. Therefore, in this study we compare the relation of FRAX® index with those of other variables, such as lean and fat mass, liver function parameters, and amount of ethanol consumed, with the presence or not of prevalent fractures in 57 chronic alcoholic men, older than 40 years, drinkers of more than 200 g ethanol/day during a long time. We found that FRAX® index was significantly higher among those with any fracture, but the same happened with BMI, total fat amount, and fat amount at arms, as well as total amount of ethanol. The FRAX® index did not show differences among those with or without vertebral fractures, or rib fractures. Patients with rib fractures showed differences in total fat amount and right arm fat amount when compared with patients without rib fractures. Therefore, these results suggest that in the alcoholic, other variables, such as amount of ethanol consumed and fat mass, should be considered, in addition to FRAX®, in the prediction of fractures.

Key words: *FRAX® index, alcoholism, bone alterations, fractures, osteopenia, body composition.*

Introduction

The alcoholic patient is exposed to a higher risk of fractures, due, essentially, to two factors: on the one hand, the reduction in bone mass, a multifactorial phenomenon, influenced by many mechanisms, such as the alcohol itself[1-5], the associated malnutrition[6,7], the eventual hepatopathy[8], the secondary hormonal alterations due both to the alcohol and the hepatopathy, and the possible effect of the pro-inflammatory cytokines; on the other hand, the kind of life the alcoholic has, which exposes these patients to falls and traumas which contribute to these fractures[9]. Today, we have clinical tools which allow us to predict the risk of fracture prospectively. One of these, currently in vogue, is FRAX®, an index which includes variables such as the body mass index (BMI), bone mineral density (BMD), age, history of fracture, family history of fracture, alcohol itself, conditions associated with osteoporosis such as hypogonadism (which also affects alcoholics), corticoids, hepatopathy, and others[10]. However, in previous studies we have seen that bone mass in alcoholics is related to lean mass and fat mass[6,11], and that various cytokines, by acting on the receptor activator for nuclear factor κ B (RANK), and its ligand RANKL[12], may also play a pathogenic role. In addition, other variables such as vitamin D[7], may have an influence on fractures, as well as certain social and personal aspects of the environment of the alcoholic, which impact on their life style and their risk of fracture and trauma. None of these parameters is directly included in FRAX®, which means that it is important to compare the value of this tool with those of the variables cited, and to analyse whether lean mass, fat mass, hepatic function, quantity of alcohol consumed, or FRAX® is associated most closely with the presence of fracture in the alcoholic patient, in a cross section of a population with a certain number previous fractures. This is the objective of this work, part of a wider prospective study designed to analyse the relative value of the aforementioned parameters in the diagnosis of fractures occurring in this group of alcoholics followed in the long term.

Patients and methods

57 male patients over 40 years of age, who had given their informed consent, and who had been consecutively admitted to the internal medicine service of our Centre due to organic problems related to the excessive consumption of alcohol, drinkers of great quantities of alcohol (210 ± 90 g/day) over 31 ± 9 years, were included, adapting the FRAX® criteria, designed for the evaluation of risk of fracture in individuals over the age of 40 years. The patients included in this study had sustained significant after effects as a result of their chronic consumption of alcohol: thirty three were cirrhotic, 8 had neoplasms, and 22 died within a period of 18 months (inter-quartile rate 11-56 months) from their inclusion in the study.

X-rays (Xr) of the post-anterior (PA) and lateral (L) thorax were carried out in order to evaluate the presence of rib fractures, while in the lateral Xr we were looking for dorsal vertebral fractures, applying morphometric criteria[13]. To this we added a detailed anamnesis, to see whether or not they had earlier fractures. In some cases it was not possible to correctly evaluate the Xr in the thorax. We also performed a densitometric study using double energy X-ray absorptiometry (DXA) with a LUNAR densitometer (GE HealthCare), to evaluate bone mass in different parts of the skeleton (bones of upper limbs, lower limbs, ribs, spine, pelvis and total), and the T-score in the spinal column and hip. Using these T-score values we grouped our patients as osteoporotic, osteopenic or normal, according to the criteria currently in use[14].

We carried out a nutrition assessment including, in addition to the aforementioned densitometric parameters, a previously validated subjective scale of nutritional assessment, which is based on the qualitative assessment of the lean mass and fat mass in the abdomen, upper and lower limbs, temporal muscle and Bichat's ball[15]. We calculated FRAX® in all the cases[10].

A routine analysis was carried out in all patients, which included albumen, prothrombin activity and blood bilirubin, as well as determining IGF-1 (chemoluminescence, DPC, Los Angeles, CA, USA), 1-25 dihydroxyvitamin D3 (radioimmunoanalysis, Nichols, San Juan de Capistrano, CA, USA), and parathyroid hormone (PTH, immunochemiluminescence, Siemens, Munich, Germany).

This study had the approval of the Ethics Committee of the University Hospital of the Canary Islands. It forms part of a wider prospective study designed to analyse the relative value of the aforementioned parameters in the diagnosis of fractures occurring in this group of alcoholics followed over the long term.

Statistical method

We calculated the difference existing between patients with and without existing fractures in relation to the FRAX® index, lean mass, fat mass, nutritional assessment, and analytical parameters related to hepatic function. Through the Kolmogorov-Smirnov test we determined whether the variables studied were adjusted or not to a parametric distribution. The tests used to compare differences between two groups were the student's T test, and the Mann-Whitney U test in the case of a non-parametric distribution of the variable analysed. To determine which variables were independently related to the FRAX® index we carried out multivariant analysis, introducing lean mass, fat mass, age, prothrombin, albumin, bilirubin, FRAX® index, BMI and subjective nutritional assessment.

Results

Thirty two of the 57 patients studied had had at least one fracture. In 4 cases this fracture was related to a serious trauma (in general, traffic accidents): 1 fracture of the tibia, another of the tibia and fibula, another of both hips, and the other of lumbar vertebrae and multiple ribs. In the thoracic Xr 24 old rib fractures were identified (as opposed

Table 1. Differences between patients with or without fractures (all types of fractures included)

	With fracture (n=32)	Without fracture (n=24)	T (Z); p
Age (years)	53.94 ± 8.81	54.21 ± 11.03	T=0.10; NS
Body mass index	24.79 ± 3.23	27.05 ± 4.29	T=2.04; p=0.047
FRAX® index	4.14 ± 2.27	2.30 ± 1.28	T=3.7; p<0.001
Daily alcohol consumption (g)	214 ± 88	203 ± 98	T=0.42; NS
Years of consumption	33.03 ± 8.51	28.30 ± 8.01	T=1.98; p=0.053
Vitamin D (pg/ml)	28.00 ± 16.87	31.85 ± 14.23	T=0.79; NS
IGF-1 (ng/ml)	99.7 ± 104.6 47.1 (27.9-183.60)	67.8 ± 44.85 48.3 (32.9-105.0)	Z=0.21; NS
PTH (pg/ml)	90.23 ± 132.01 51.40 (29.83-86.23)	60.62 ± 47.37 49.0 (26.25-82.40)	Z=0.56; NS
Prothrombin (%)	75.46 ± 22.13	68.98 ± 27.90	T=0.92; NS
Albumin (g/dl)	3.29 ± 0.57	3.29 ± 0.82	T=0.03; NS
Bilirubin (mg/dl)	3.61 ± 3.65 2.5 (1.1-6)	4.43 ± 4.60 2.35 (1.2-5)	Z=0.73; NS
Total BMD (g/cm^2)	1.07 ± 0.10	1.08 ± 0.095	T=0.59; NS
T-score total hip	-1.28 ± 1.09	-0.83 ± 1.10	T=1.52; NS
T-score L2-L4	-1.39 ± 1.15	-1.39 ± 1.16	T=0.38; NS
Total lean mass (g)	50.085 ± 5.145	53.052 ± 7.653	T=1.64: NS
Total fat mass (g)	17.704 ± 6.620	22.584 ± 9.656	T=2.12; p=0.039

The data are expressed as the mean ± standard deviation, and were compared using the student's T test (T). After the application of the Kolmogorov-Smirnov test it was observed that some variables did not adjust to a parametric distribution. In these cases, in addition to the mean and standard deviation the median and, in brackets, the interquartile range were also provided, and the two groups (with or without fractures) were compared using the Mann-Whitney U test (Z)

to 20 without fracture) and in the spinal Xr, 13 (as against 25). In Tables 1-3 the data from patients with or without fractures in the different locations analysed is summarised. As we see, the total fat mass was greater in those who did not have fractures (any fracture, not even of the rib), and the same for BMI, and marginally, those patients who had been drinkers for longer also had more fractures.

It is notable that in no case was the total BMD significantly different between patients with or without previous fractures. With the variables already mentioned we carried out a logistic regression study to see which factors could be independently related to fractures. We found that, although, with respect to any fracture, the factors to which they were independently related were, first the FRAX® index, then prothrombin activity and lastly the duration of (alcohol) intake in years (Table 4), in relation to rib fractures the first parameter to which it was independently related was total fat mass (Table 5). It is also worth highlighting the fact that none of the parameters chosen played an independent role in relation to the presence or absence of vertebral fractures.

In Figures 1 and 2 we show the ROC curves which illustrate the global capacity of the fat mass and the FRAX® index to diagnose any fracture (1a and 1b) and rib fracture (2a and 2b). As can be seen, FRAX® is useful in both cases, especially to diagnose any osteoporotic fracture, while in the fat area it is only the rib fracture which is diagnosed.

Discussion

The FRAX® index is a widely used index for the diagnosis of risk of fracture[10]. It is, therefore, a prognostic index, and it is as such that it should

Tabla 2. Patients with or without rib fractures

	With fracture (n=24)	Without fracture (n=20)	T (Z); p
Age (years)	52.96 ± 8.33	54.90 ± 12.15	T=0.63 ; NS
Body mass index	24.78 ± 3.36	27.04 ± 3.97	T=2.05; p=0.047
FRAX® index	3.76 ± 1.93	3.04 ± 2.30	T=1.14; NS
Daily alcohol consumption (g)	217 ± 94	198 ± 96	T=0.68; NS
Years of consumption	31.96 ± 6.57	32.15 ± 11.20	T=0.70; NS
Vitamin D (pg/ml)	26.86 ± 16.07	33.86 ± 15.97	T=1.36; NS
IGF-1 (ng/ml)	108.2 ± 112.5 47.1 (28.4-191.0)	80.6 ± 61.13 53.5 (32.9-118.2)	Z=0.04; NS
PTH (pg/ml)	58.37 ± 44.35 45.60 (28.7-85.4)	82.18 ± 80.93 52.8 (30.55-95.68)	Z=0.85 ; NS
Prothrombin (%)	77.69 ± 22.05	71.03 ± 27.44	T=0.79; NS
Albumin (g/dl)	3.35 ± 0.56	3.28 ± 0.73	T=0.38; NS
Bilirubin (mg/dl)	3.18 ± 2.42 2.25 (1.23-5)	4.33 ± 4.54 3.20 (1.1-5.6)	Z=0.73; NS
Total BMD (g/cm^2)	1.06 ± 0.11	1.07 ± 0.08	T=0.23; NS
T-score total hip	-1.33 ± 1.10	-0.88 ± 0.86	T=1.49; NS
T-score L2-L4	-1.38 ± 1.25	-1.54 ± 0.87	T=0.19; NS
Total lean mass (g)	50.321 ± 5.201	53.063 ± 8.136	T=1.38: NS
Total fat mass (g)	17.015 ± 6.250	21.671 ± 8.827	T=2.00; p=0.052

The data are expressed as the mean ± standard deviation, and were compared using the student's T test (T). After the application of the Kolmogorov-Smirnov test it was observed that some variables did not adjust to a parametric distribution. In these cases, in addition to the mean and standard deviation the median and, in brackets, the interquartile range were also provided, and the two groups were compared using the Mann-Whitney U test (Z)

be considered, although it is obvious that the same factors which allow one to predict a future fracture ought also to be capable of differentiating between patients with or without fractures at any given moment. In this work we have analysed the capacity of this index to detect these differences in alcoholic patients, since in this group there is a series of factors which may distort its value. There is no doubt as to the existence of osteopathy in the chronic alcoholic. Already observed by Saville in the 1960s[16], Oppenheim[9] subsequently applied the term "battered alcoholic syndrome" to those alcoholic patients with more than three fractures in different states of consolidation. Later, the classic works of Israel[1], Diamond[2] and others[17-19], to cite only a few, serve only to confirm that in alcoholics, independently of cirrhosis, there is a metabolic osteopathy characterised by osteopenia, in which malnutrition plays a significant role[6,20]. This is due, above all, to defective bone formation, although there being some controversy with respect to reabsorption, which expresses an imbalance between the formation and destruction of bone. But certain aspects, on which we comment below, make this different. Firstly, age: alcohol reduces life expectancy, and osteoporosis in the alcoholic, although increasingly serious with age, appears much earlier than when associated with the menopause, for example, or with senility. Secondly, the nutritional state. This is often clinically evaluated in a general way, through BMI, or subjectively, but without paying attention to the fat or lean areas of the body which may be altered selectively; it is common for some alcoholics to have a relative increase in fat mass accompanied by a parallel decrease in lean mass, with a

Tabla 3. Patients with or without dorsal fractures

	With fracture (n=13)	Without fracture (n=25)	T (Z); p
Age (years)	56.15 ± 9.67	54.48 ± 10.52	T=0.48 ; NS
Body mass index	27.39 ± 4.09	26.28 ± 3.86	T=0.74; NS
FRAX® index	4.17 ± 2.69	2.96 ± 1.67	T=1.71; NS
Daily alcohol consumption (g)	202 ± 130	223 ± 91	T=0.53; NS
Years of consumption	35.77 ± 10.64	29.33 ± 7.43	T=2.08; p=0.046
Vitamin D (pg/ml)	30.30 ± 18.70	34.14 ± 18.64	T=0.56; NS
IGF-1 (ng/ml)	89.1 ± 74.8 53.5 (33.8-152.1)	81.7 ± 99.0 46.9 (30.4-91.2)	Z=0.53; NS
PTH (pg/ml)	82.45 ± 93.32 55.10 (27.02-93.05)	99.99 ± 143.18 55.0 (42.25-92.20)	Z=0.62; NS
Prothrombin (%)	74.00 ± 24.47	70.91 ± 21.14	T=0.39; NS
Albumin (g/dl)	3.55 ± 0.77	3.17 ± 0.59	T=1.61; NS
Bilirubin (mg/dl)	3.63 ± 3.61 2.2 (1.0-5.3)	4.49 ± 5.09 2.75 (1.15-5.88)	Z=0.30; NS
Total BMD (g/cm^2)	1.07 ± 0.10	1.10 ± 0.10	T=0.69; NS
T-score total hip	-1.09 ± 1.25	-0.98 ± 1.12	T=0.28; NS
T-score L2-L4	-1.79 ± 1.18	-1.14 ± 1.34	T=1.48; NS
Total lean mass (g)	51.271 ± 7.673	51.947 ± 5.149	T=0.30: NS
Total fat mass (g)	23.778 ± 9.270	20.682 ± 7.301	T=1.09; NS

The data are expressed as the mean ± standard deviation, and were compared using the student's T test (T). After the application of the Kolmogorov-Smirnov test it was observed that some variables did not adjust to a parametric distribution. In these cases, in addition to the mean and standard deviation the median and, in brackets, the interquartile range were also provided, and the two groups (with or without fractures) were compared using the Mann-Whitney U test (Z)

normal or even raised BMI (malnourished obesity). This is important since although the decrease in lean mass reduces bone formation[21], the fat may exert opposing effects, since, although contributing to the weight, and thus increasing the bone mass, it may also be the source of cytokines which can cause bone lesions, such as tumour necrosis factor (TNF)[22]. It is also notable that the total fat mass replaces the FRAX® index in its capacity to diagnose existing fractures at any given moment. As we have just indicated, the fat mass, which may be elevated in the alcoholic, contributes significantly to total weight. It is this weight which is opposed to gravity, and which our skeleton has to support, which exerts a stimulating effect on osteoformation. But it is also worth noting that we did not see a relationship between fracture and lean mass. Lean mass determined by densitometry may be misleading in the alcoholic since the presence of ascites or oedemas may falsify the results[23]. In this study we cannot discount the influence of hydrosaline retention, although generally the densitometry was carried out when the patient was ready to be discharged, or, at least, a few days after treatment.

A third factor to consider in the osteopathy of the alcoholic is hormonal alterations. This is due in part to the cirrhosis, although the alcohol in itself, without the need for the coexistence of cirrhosis, provokes hypogonadism, altering the levels of vitamin D and the cortisol metabolism, even though the effects of these hormones are contained, in one way or another, in the FRAX® index.

FRAX® is, without a doubt, a useful tool. In fact, if we consider its value in the diagnosis of

Table 4. Logistic regression in successive steps, which shows that the FRAX® index (FRAXfrac), the activity of prothrombin (ptbna) and the year of consumption of alcohol (tconsumo) are the only parameters which hold an independent relationship with the presence of any fracture

Fracture (total)				
		B	**Wald**	**Sig.**
Step 1(a)	FRAXfrac	-1.398	8.330	0.004
	Constant	3.161	6.275	0.012
Step 2(b)	ptbna	-0.067	5.800	0.016
	FRAXfrac	-2.225	9.257	0.002
	Constant	10.592	7.820	0.005
Step 3(c)	Ptbna	-0.069	5.464	0.019
	tconsumption	-0.136	3.501	0.061
	FRAXfrac	-2.598	7.040	0.008
	Constant	15.688	7.851	0.005

a) Variable(s) introduced in step 1: FRAXfrac. b) Variable(s) introduced in step 2: ptbna.
c) Variable(s) introduced in step 3: tconsumption

Table 5. Logistical regression in successive steps which shows that the only parameter which shows an independent relationship with the presence or absence of costal fractures is the total quantity of fat (totfatab)

Rib Fracture				
		B	**Wald**	**Sig.**
Step 1(a)	totfatab	0.000	4.115	0.042
	Constant	-2.234	5.010	0.025

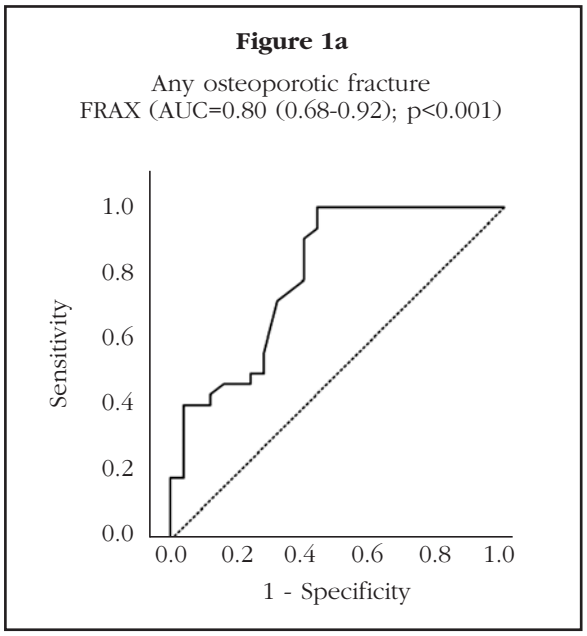
a) Variable(s) introduced in step 1: totfatab

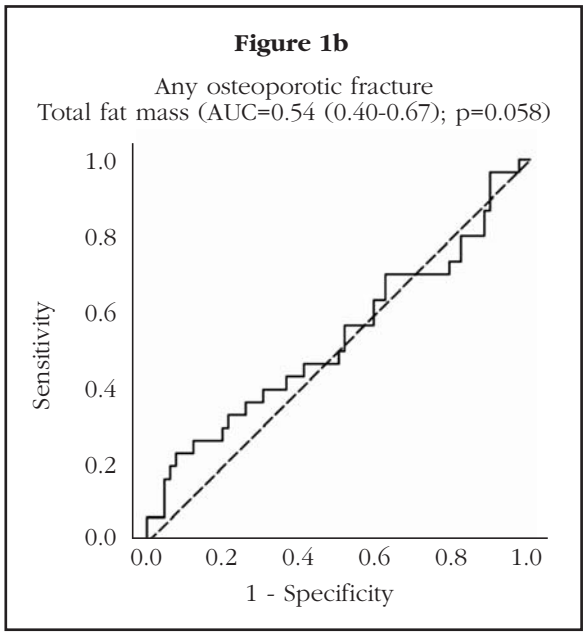
any type of fracture, those for which FRAX® should really be used to make a prognosis, we see that the ROC curve shows an area below the curve of 0.8, which is to say, acceptable enough, and better than that obtained when the diagnostic value of other variables is explored. However, our study, still preliminary, does not allow us to infer conclusions about the prognostic role of FRAX®.

It is notable that, in relation to costal fractures, it is the fat mass which replaces the other variables. In an earlier work we found that what was really associated with costal fractures was irregular eating and disordered life-style[24], in summary, the "marginality" of the inveterate alcoholic, at least in our environment. The finding of a higher number of fractures in widowers and men who are separated, as has been referred to years ago by Keso et al.[25], may be interpreted in the same way. The fact that fat mass is now being related to fracture may also be interpreted in this way, in that marginality and solitude results in a worse nutritional state, with a decrease in fat (and lean) mass and a life-style with a propensity to traumatic fracture.

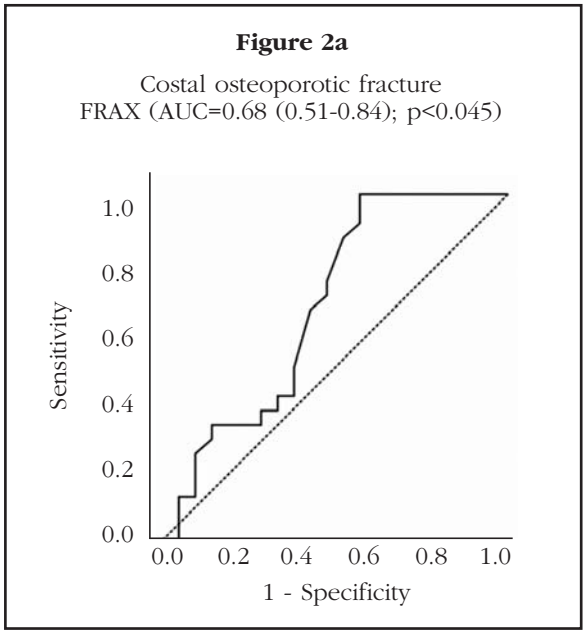
In conclusion, FRAX® also appears to be a useful tool in the prediction of risk of fracture in the alcoholic patient, even though its predictive capacity in these patients is still to be determined. However, the fact that fat mass replaces the FRAX® index in the diagnosis of costal fractures obliges us to take into account that the detailed analysis of the composition of the body, not contemplated in the FRAX® index, may need to be considered in the prognostic evaluation of fractures in these patients.

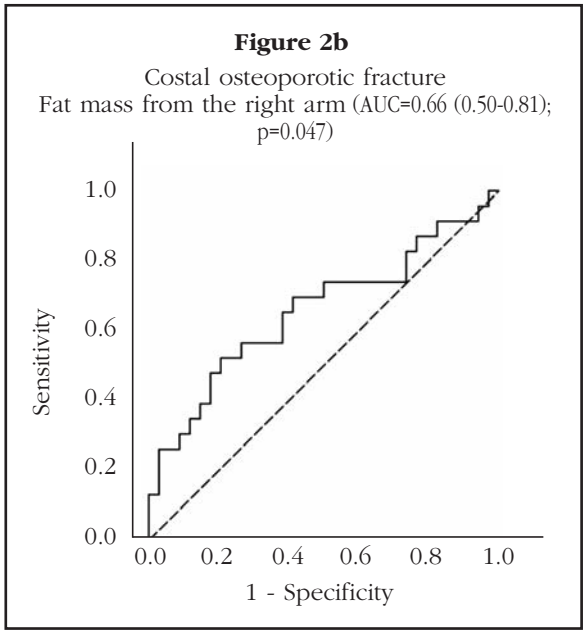
Figured 1a and 2b. ROC curves which illustrate the specificity and sensitivity of FRAX® and fat mass in the diagnosis of any osteoporotic fracture





Figures 2a and 2b. ROC curves which illustrate the specificity and sensitivity of FRAX® and fat mass (from the right arm) in the diagnosis of costal osteoporotic fracture





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