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On the Behaviour of the Fructose Concentration During Therapy of Infertile Men

Zachowanie się stężenia fruktozy w nasieniu podczas leczenia niepłodnych mężczyzn

Fructose occurring in the plasma of human semen is produced by the epithelium of seminal vesicles. Huggins and Johnson (1) were the first who found sugar originating from the seminal vesicles in the semen of man. Mann (4) proved that the sugar is not glucose but fructose.

Seminal fructose is produced in the seminal vesicles from blood glucose (4). Mann's opinion is that the concentration of fructose in seminal vesicles is three times higher than that in blood. The fructose formation depends on the presence of testosterone which is produced by Leydig cells in testicles. On the ground of the above fact, Mann (4) suggested a "fructose test" as a basis for the estimation of the hormonal activity of testicles. Fructose appears after the period of sexual maturation and disappears when castration is performed. Vicarious administration of testosterone cause the repeated occurrence of fructose in the seminal plasma (3, 6).

Landau and Loughead (3) in the Kenyon Clinic in Chicago performed identical examinations as those made by Mann, proving that men displaying a low secretion of testical androgens had also a decreased concentration of fructose in the semen. Eunuchs, to whom testosterone had been administered, showed normal values of fructose concentration in the seminal plasma. The authors drew the conclusion that there was a close correspondence between the amount of testosterone administered and the level of fructose in the semen. Clinical observations of American research workers, which stemmed from the ideas and discoveries of Mann, created new and important exploratory aspects for Clinics dealing with human infertility.

The metabolism of human and certain mammalian (bull, ram) spermatoza is based on *fructolysis*. Mann (4) indicates that the survival and motility of spermatozoa in the absence of oxygen is possible only due to anaerobic *fructolysis*. In the presence of oxygen, the influence of fructose on spermatozoa is less clear because oxygen is the cause of endogenous respiration which is sufficient to produce the movement of spermatozoa; but some slight *fructolysis* processes take place even in these circumstances (4, 14).

EXPERIMENTAL

The examination of 140 men who sought medical advice because of matrimonial infertility, was carried out at the Andrologic Outpatient Department. Threefold examinations of each patient's semen were performed (before the treatment, in the course of treatment and after the treatment). The samples of semen were obtained by masturbation. The sexual abstinence of the patients lasted in the most cases 6 to 8 days. The sexual life, general clinical state of the patient and the clinical state of the patient's sexual organs were taken into account. The amount of fructose in the seminal plasma was determined by R o e's method in N a d w o r n y's modification (5) *.

Table 1. Genital organ and fructose

	Clinical state of genital organ					
	Normal	Testicles-of hazel nut size	Testicles-of plum size-soft	Varicocoele of seminal funiculus	Enlargement of tecticles	Swelling of seminal funiculus
Fructose in μ/ml.	850—5300	400—3700	750—3500	700—4100	1700—4300	1500—4300
Number of cases	80	14	7	13	7	19

The results of the determination of fructose concentration in the semen were collated with the clinical state of the sexual organs, the morphologic examination of the semen and results of applied therapy. Taking into consideration the state of the testicles, epididymis and seminal cord, the group of 140 men was divided into 6 classes. The concentration of fructose as a function of the clinical state of the sexual organs is presented in Table 1. A comparison of fructose concentration and the clinical state of the sexual organs indicates the existence of a certain inter-dependence. In most cases (78%), out of 14 patients who had small testicles, decreased values (below 1200 γ/1 ml of semen) of the concentration of fructose were found. 75 men, out of 80 (93.3%) who had normal

* The method was described in detail in the paper: "The influence of Age, Occupation and Diseases Suffered on the Concentration of Fructose in the Semen". Ann. Univ. M. Curie-Skłodowska, Sec. D, **21**, 51—59, 1966.

sexual organs, showed the concentration of fructose within the normal limits. In 5 patients (6.7%) who showed a decreased fructose concentration in the semen, no pathological changes were found in their sexual organs, so the decrease was caused by other diseases. A comparison of the volume of the semen and the concentration of fructose in it, performed with 140 patients, shows also a certain regularity. With the patients whose volume of semen was lower than 1 ml, a decreased concentration of fructose in the semen was found in most cases (57%). In some cases (13.1%) a low concentration of fructose was found in the semen of the patients with the volume of semen within 1—4 ml. On the other hand, in all the patients (26 cases) with the volume of semen over 4 ml., the concentration of fructose exceeded 1400 γ/1 ml. The above data are presented in Fig. 1. The concentration of fructose was also compared with the morphology of semen. Here the Johansson classification concerning the morphologic distribution of semen was applied. Collected material contained both low values of the concentration of fructose and decreased and normal values in case of *normospermia, oligospermia* I° and II°, *cryptospermia* and *azoospermia.* Low values were not found in men with *asthenospermia* and *necrospermia.* It is worth noticing though, that in most cases the low concentration of fructose was observed in men with *azoospermia* and *oligospermia,* but it was seldom found in *normospermia.* Among 40 men with *normospermia* there were 37 cases of normal concentration of fructose (92.5%) and only 3 of them (7.5%)

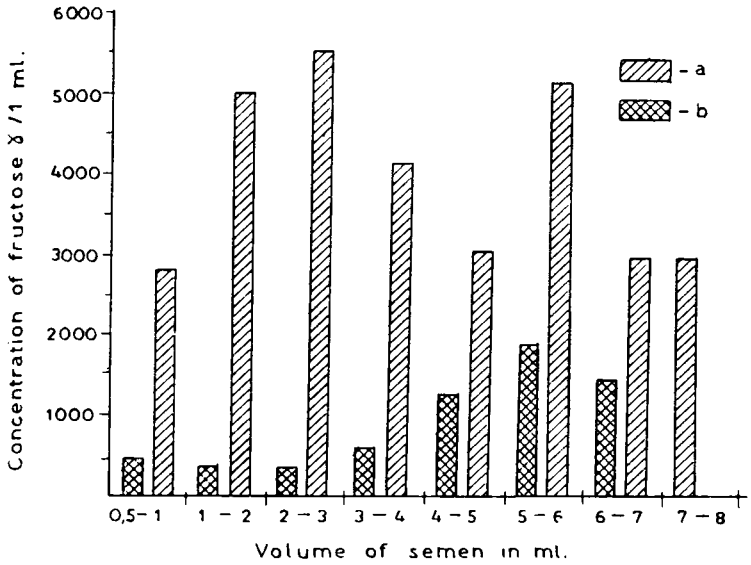


Fig. 1. The volume of semen vs. fructose concentration; a — the highest concentration of fructose, b — the lowest concentration of fructose

showed the low concentration (600—800γ/1 ml) of semen. The highest concentrations of fructose (4000—5600 γ/ ml) were found in patients with 70—80 million of spermatozoa in 1 ml of semen. Medium values of fructose concentration occurred when the amount of spermatozoa were within the limits of 60—70 million per 1 mililiter of semen. Men with a number of spermatozoa over 100 million displayed fructose concentration within the limits of 1700—2400 γ/1 ml. of semen. Figure 2 presents the dependence of the concentration of fructose and the morphology of semen.

Following the morphologic examination of semen, the patients who showed abnormalities were directed to the Andrologic Outpatient Department for treatment. Therapy was also attempted when the examinations revealed the deficiency of spermatozoa or spermatogenous cells in ejaculates.

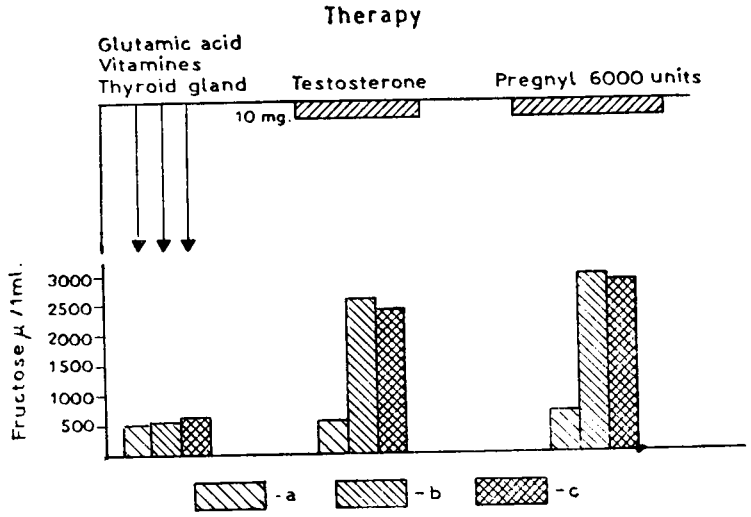


Fig. 2. The results of the therapy of Leydig cells insufficiency in *normospermia;* a — fructose before therapy, b —fructose on the 14th day of treatment, c — fructose on the 28th day of treatment

In such cases an advantageous influence on the psychic state of the patient was taken into account. A scheme of the therapy of infertile men was prepared thoroughly. Table 2 indicates the method of treatment of infertile men. Pregnyl was administered twice a week in doses of 1000 units; vitamin E — three times a day in doses of 0.1 g. and glutamic acid in doses of 4—6 g per day; Thyroid preparations — once a day in tablets containing 0.006 mg. of iodine. Testosterone was injected intramuscularly every second day in doses of 10 mg. This therapy lasted

2—4 weeks. Among 40 cases of *normospermia,* with 20 of them the concentration of fructose increased, the motility of spermatozoa improved and the amount of pathological forms decreased distinctly. The increase of the concentration of fructose in the patients' semen was especially significant in cases where pregnyl and testosterone were administered (10 cases). On the other hand, the patients treated with thyroid preparations, vitamins and glutamic acid showed only in some cases a slight increase of the concentration of fructose (the increase of 100—200 γ/1 ml. of semen).

Table 2. The therapy of infertile men

Morphology of semen	Therapy						Number of patients
	Pregnyl	Pregnyl and testosterone	Glutamic acid, vitamins A+D, E	Glutamic acid, ferrum, vitamins	Thyroid gland, vitamins	Testosterone, vitamins	
Normospermia	5	—	40	10	5	5	40
Oligospermia I°	11	—	—	—	21	10	42
Oligospermia II°	4	—	—	—	6	4	14
Cryptospermia	4	—	—	—	—	6	10
Asthenospermia	—	—	2	—	6	4	12
Azoospermia	8	—	16	—	4	4	16
Necrospermia	—	6	6	—	—	—	6
Total							140

Among 100 patients of other groups (*oligospermia* I° and II°, *cryptospermia, asthenospermia, azoospermia* and *necrospermia*), 78 of them did not show any increase of fructose concentration and 22 — only slight increase of the fructose level in the semen. Increase of the fructose concentration took place only in cases where testosterone and pregnyl were administered. Thyroid preparations, vitamins, glutamic acid and ferrum had no influence on the concentration of fructose, though the morphology of semen improved.

DISCUSSION

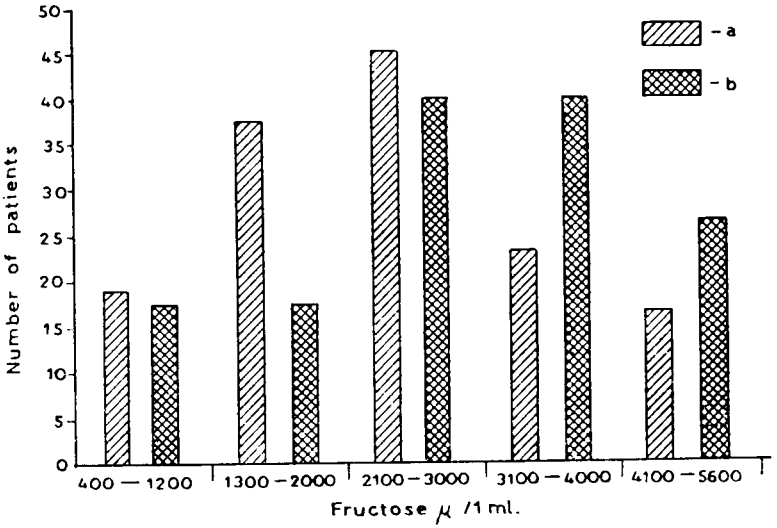
The results presented above indicate that the patients with abnormalities in the clinical state of the sexual organ show also low values of fructose concentration (below 1200 γ/1 ml.) in the semen. There are only few exceptions from this rule. Similar observations were made by Ritzman and Schirren (9, 11). Poczekaj and Wenclewski (8) examined 48 men but found no close dependence between the clinical state of the sexual organ and the concentration of fructose in the semen.

I noticed also some cases of a low concentration of fructose in men whose sexual organs showed no pathological changes. Identical observations were made by Ritzman and Schirren (9, 11) who explained that the cause of the low concentration of fructose in the semen might be an isolated disease of seminal vesicles or metabolic disturbances. Some conclusions can be drawn from the comparison of the concentration of fructose, the volume of semen and the number of spermatozoa. Low values of the semen volume occurred along with the low concentration of fructose, while high concentrations of fructose were accompanied by the volume of semen over 4 ml. Vasterling and Schirren (14, 11) did not report this dependence. It is worth noticing that the low concentrations of fructose were found in patients with *azoospermia, oligospermia* and only in some cases of *normospermia* (12). Kimming and Nikolowski (2, 6) pointed out high concentration of fructose in men with normal spermiogram; in most cases it proved that the semen was normal. The best results were obtained with hormone preparations used in the treatment of endocrine insufficiency of the testicle (13). In such cases, administration of hormones (pregnyl and testosterone), resulted in an increase of the concentration of fructose in the semen. Figure 2 indicates the results of the therapy of patients with insufficiency of Leydig cells in the case of *normospermia*. The administration of vitamins, thyroid hormone and glutamic acid influenced the motility of spermatozoa and caused a decrease of the pathological forms of spermatozoa in the semen, but did not affect the concentration of cructose in the semen.

According to Nowakowski and Schirren (7, 11) patients with *normospermia* and low concentration of fructose in semen, who show an increase of fructose concentration following therapy by means of testosterone and chorional gonadotrophin, are examples of the patients in whom insufficiency of the Leydig cells developed after the period of puberty. The cause of the above mentioned fact may be either insufficiency of ICSH which led to the insufficiency of Leydig cells (3, 9, 11) or a lesion of Leydig cells. Another explanation is to be assumed in the case of *normospermia* or the pathological semen morphology with simultaneous decrease of the fructose concentration which cannot be cured with gonadotropins and testosterone. Nowakowski and Schirren (7, 11) presumed that disturbances of fructose synthesis in semen occurred in these patients because of seminal vesicles diseases or the diseases due to metabolism. Men with considerable anatomical changes in the testicles or lesions in the morphology of semen and at the same time showing a low concentration of fructose in the semen, display not

only lesion of the urethral apparatus but also lesion of the interstitial part of the testicle.

Men with normal values of fructose concentration in the semen after the therapy showed only sligthly increased concentrations. The most probable explanation of the fact is that the endocrine part of the testicles and seminal vesicles were efficient and sufficiently stimulated by androgenes of their own and, therefore, hormone administration did not influence the concentration of fructose in the semen (11, 13, 14). Figure 3 presents the concentration of fructose before and after treatment.



Fig; 3. The concentration of fructose in semen before and after therapy; a — number of patients before therapy, b — number of patients after therapy

The determination of fructose in the semen plays an important part in the clinical diagnosis of the endocrine activity of testicles. However, the concentration of fructose cannot be the basis for the estimation of the functional state of testicles, as is the case in bilateral disease of testicles when advanced changes are present. It is also difficult to find the extent of endocrine disturbances of male gonads. The feebleness or cessation of Leydig cells activity is usually accompanied by the cessation of the accessory glands activity (seminal vesicles, Cowper's glands). The second question is the occurrence of *normospermia* along with the decreased concentration of fructose. In these cases, the normal spermiogram is not a proof of an undamaged testicle. There might be a hormonal insufficiency of the testicle which did not cause the morphologic changes of semen.

Therefore the microscopic examination of the ejaculate should be completed by quantitative determination of fructose in the semen so that our opinion on the activities of the testicles might be as complete as possible.

CONCLUSIONS

1. Examination of the concentration of fructose in semen should be completed by the morphologic examination of semen in infertile men.
2. In the case of endocrine insufficiency good therapeutic results were obtained by administration of hormones: pregnyl and testosterone.
3. Vitamins, thyroid preparations and glutamic acid did not show any clear influence on the therapy of Leydig cells insufficiency, but on the other hand, these preparations caused a distinct increase of the quantity of spermatozoa, of the percentage of motile and normal forms.
4. Determination of the concentration of fructose and the morphologic examination of semen is a sufficient test for diagnosing generative and endocrine insufficiency of testicles.
5. In order to find the cause and type of insufficiency, the biopsy of the testicle, the determination of the concentration of gonadotrophic hormones and fractional determination of steroids in the urine is necessary.

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Zachowanie się stężenia fruktozy w nasieniu podczas leczenia niepłodnych mężczyzn

Streszczenie

Badania przeprowadzono u 140 mężczyzn w Wojewódzkiej Przychodni Andrologicznej w Lublinie określając stan kliniczny narządu płciowego, morfologię nasienia oraz stężenie fruktozy w plazmie nasienia. Miały one na celu ustalenie zależności poziomu fruktozy od wewnątrzwydzielniczej czynności jądra.

Materiał badawczy podzielono na 3 zasadnicze grupy:

1. Do pierwszej grupy zaliczono 19 (13,7%) przypadków z niskim poziomem fruktozy w nasieniu, poniżej 1200 γ/1 ml.
2. W drugiej grupie znajduje się 37 (26,3%) przypadków z obniżonym poziomem fruktozy 1300—2000 γ/1 ml.
3. Grupa trzecia obejmuje 84 (60%) przypadki z wartościami fruktozy w granicach prawidłowych — powyżej 2000 γ/1 ml.

W leczeniu niedomogi wewnątrzwydzielniczej jądra najkorzystniejsze wyniki uzyskano stosując hormony: pregnyl i testosteron. Podawanie witamin, hormonu tarczycy oraz kwasu glutaminowego nie prowadziło do podwyższenia stężenia fruktozy w nasieniu, a miało wpływ na zwiększenie liczby ruchliwości i zmniejszenie odsetka postaci patologicznych plemników. Autor wyraża opinię, że ilościowe oznaczenia fruktozy w nasieniu przedstawia godny polecenia test w ocenie wewnątrzwydzielniczej czynności komórek Leydiga, z pomocą którego można wnioskować o hormonalnej aktywności jąder.

Ryc. 1. Objętość nasienia a poziom fruktozy; a — najwyższe stężenie fruktozy, b — najniższe stężenie fruktozy.

Ryc. 2. Wyniki leczenia w normospermii z niedomogą komórek Leydiga; a — fruktoza przed leczeniem, b — fruktoza w czternastym dniu leczenia, c — fruktoza w 28 dniu leczenia.

Ryc. 3. Fruktoza w nasieniu przed i po leczeniu: a — liczba pacjentów przed leczeniem, b — liczba pacjentów po leczeniu.

Tab. 1. Narząd płciowy a fruktoza.

Tab 2. Leczenie niepłodnych mężczyzn.

Исследование концентрации фруктозы в плазме семени при лечении мужского бесплодия

Резюме

Исследованы 140 мужчин — пациентов андрологической консультации, у которых определяли клинический статус половых органов, морфологию семени и концентрацию фруктозы в семенной плазме.

Целью исследований было установление зависимости уровня фруктозы от внутрисекреторной деятельности семенной железы.

Исследуемые были разделены на 3 группы:

первую группу составляли 19 мужчин (13,7%) с низким уровнем семенной фруктозы (ниже 1200 гамма/мл);

вторую — 34 мужчины (26,3%) с пониженным уровнем фруктозы (1300—2000 гамма/мл);

третью — 84 мужчины (60%) с нормальным содержанием фруктозы (выше 2000 гамма/мл).

Наиболее эффективный исход лечения внутрисекреторной недостаточности яичка был получен после применения гормонов прегниля и тестостерона. Введение витаминов, гормона щитовидной железы и глютаминовой кислоты не повышало концентрации фруктозы в семени, но влияло на увеличение числа и деятельности сперматозоидов, а также понижало процент их патологических форм.

Таким образом, определение содержания фруктозы в семени, свидетельствующее о гормональной активности семенной железы, является, по мнению автора, необходимым при оценке внутрисекреторной функции клеток Лейдига.

Рис. 1. Объем семени и концентрация фруктозы.
Рис. 2. Результаты лечения нормоспермии с гипофункцией клеток Лейдига.
Рис. 3. Концентрация фруктозы в семени до и после лечения.
Табл. 1. Половые органы и концентрация фруктозы.
Табл. 2. Лечение бесплодия у мужчин.

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