JCI The Journal of Clinical Investigation

THE ORIGIN AND NATURE OF NORMAL HUMAN SYNOVIAL FLUID

Marian W. Ropes, … , Elsie C. Rossmeisl, Walter Bauer

J Clin Invest. 1940;19(6):795-799. https://doi.org/10.1172/JCI101182.

Research Article

THE ORIGIN AND NATURE OF NORMAL HUMAN SYNOVIAL FLUID [1, 2]

By MARIAN W. ROPES, ELSIE C. ROSSMEISL, AND WALTER BAUER

(From the Medical Clinic of the Massachusetts General Hospital, the Department of Medicine, Harvard Medical School, and the Massachusetts Department of Public Health, Boston)

(Received for publication June 10, 1940)

In a previous communication (1) the physical and chemical properties of normal bovine synovial fluid were described and their significance discussed. From these data it was concluded that normal bovine synovial fluid is a dialysate of plasma containing albumin, globulin and mucin. A similar characterization of normal human synovial fluid has been made in order to determine whether its origin and nature are the same. The information obtained from normal human fluid will afford a basis for a comprehensive evaluation of pathological synovial fluids.

METHODS

The synovial fluids were obtained immediately after death from the knees of patients who had had no signs or symptoms of joint disease. The fluid was withdrawn through an eighteen-gauge lumbar puncture needle inserted distal to the patella. Blood was withdrawn from the heart at the same time. The analytical methods were those used in the study of normal cattle fluid (1). Albumin and globulin contents were determined by the method of Butler and Montgomery (2). The cytological studies on some of these fluids have already been reported (3).

RESULTS

In the present investigation 124 normal human synovial fluids were studied. The number of analyses made on any one fluid was of necessity limited because of the small amount of fluid available. By examining a large number of fluids we were able to make a sufficiently detailed characterization of normal human synovial fluid to determine that human and bovine synovial fluids are essentially alike.

In the previous series (3), amounts of fluid varying from 0.13 to 2.0 cc. were aspirated from normal human knee joints, the average amount being 0.45 cc., whereas in this series the range is from 0.13 to 3.5 cc., with an average of 1.1. If edema is present, the quantity of synovial fluid is usually increased. The fluid is a clear, pale yellow, viscous liquid, the relative viscosity of which is higher than that of normal cattle fluid. The range is from 51 to 403 with an average of 150 at 25° C. In edematous patients the synovial fluid viscosity is markedly reduced, with an average of 53 and variations from 6 to 174.

The average content of total solids is 3.41 grams per 100 grams, with variations from 2.40 to 4.83. The figures correspond with those found by Horiye (4) for postmortem fluids (1.20 to 3.93 per cent), but average slightly lower than the value given by Fisher (5) (4.4 per cent). The specific gravity was determined only in cases in which the volume of fluid was increased, with the result that the values represent those for edematous patients. The average specific gravity, 1.010, is identical with that of normal bovine fluid, and the average content of total solids of these fluids, 2.23 grams per 100 grams, is only slightly higher than that of cattle fluid (2.08 grams per 100 grams). This similarity would be expected from the fact that the protein content of human fluid from edematous patients (with over 2 cc. of fluid obtained from the knee joint) is essentially the same as that of cattle fluid. Horiye (4) reported specific gravities ranging from 1.008 to 1.015 for normal human fluids obtained postmortem.

The average pH of 6 fluids was 7.39 with a minimum of 7.29 and a maximum of 7.45. Horiye (4) found postmortem fluid to be weakly alkaline to litmus. Seeliger (6) reported its pH as 8.2 to 8.4. Boots and Cullen (7) found a pH of 7.34 in fluid from a patient with generalized

[1] This is publication Number 50 of the Robert W. Lovett Memorial for the study of crippling disease, Harvard Medical School.

[2] The expenses of this investigation have been defrayed by a grant from the Commonwealth Fund.

edema. Pescatori (8) studied 40 postmortem fluids and found an average pH of 7.95 with variations from 7.53 to 8.02.

Normal human synovial fluid contains fewer cells than normal bovine fluid, the average nucleated cell count being 63 per cu.mm. (3) as compared to 112 to 182 (1, 9, 10). Erythrocytes are absent. The average differential nucleated cell counts for normal human and bovine synovial fluid are as follows:

	Human fluid	Bovine fluid
	per cent	
Polymorphonuclears	6.5	2.2
Monocytes	47.9	36.4
Clasmatocytes	10.1	15.0
Unclassified phagocytes	4.9	3.9
Lymphocytes	24.6	40.1
Synovial cells	4.3	1.2
Unidentified cells	2.2	1.2

The total nucleated cell counts of this series can be compared with those reported for normal human fluids by Labor and von Balogh (11) (10 to 20 cells per cu.mm.), McEwen (12) (125 to 200 cells), and Kling (13) (10 to 50 cells).

The total protein content of normal human fluid (2.57 grams per 100 cc.) is approximately three times as high as that of normal cattle fluid. Since most of the increase is in the mucin fraction, the content of albumin and globulin is only twice as high in human fluid, being 1.72 grams as compared to 0.89 gram per 100 cc. This value is in the same range as those reported by Fisher (5) (1.6 per cent) and Horiye (4) (0.45 to 3.15 per cent) for normal human fluid. On the basis of the findings in many normal and abnormal human fluids, we would conclude that a value of 3.15 would be found only in an abnormal fluid. Cajori and Pemberton (14) reported 1.39 per cent protein in synovial fluid from a patient with generalized edema. Determination of the albumin and globulin fractions of human fluid was possible only when 2 cc. of fluid was obtained, with the result that the majority of determinations were made on fluids aspirated from edematous patients. Furthermore, the uncertainty of the absolute globulin concentration by any of the methods for fractionating the serum proteins, and the decreased accuracy of the methods in fluids of low protein content, make it difficult to establish accurate normal values for the protein fractions. The marked individual variations that were found may be due in part to analytical difficulties and in part to variation in capillary permeability. Similar variations have been found in normal cattle fluid (1) and in pathological fluids (14). In all cases, however, the globulin content was low and in one edema fluid no globulin was demonstrable. The albumin-globulin ratios tended to be high. In the one case in which only 2 cc. of fluid was obtained the ratio was 19.3, with a globulin concentration of 0.05 gram per 100 cc.

The presence of albumin and globulin in normal human fluid can be explained presumably on the basis of slight capillary permeability to proteins, as was assumed in the case of normal cattle fluid. The marked difference in albumin and globulin concentration indicates a much greater capillary permeability to albumin than to globulin. This is in accord with the findings in cattle fluid (1), with the results of the studies on the entrance of proteins into joints of rabbits (15), and with the conclusions of other workers (16, 17, 18, 19).

The mucin content of normal human fluid (0.85 gram per 100 cc.) is much higher than that of fluid from the astragalotibial joints of cattle, as would be expected from the marked differences in viscosity. Fisher (5) found 1.95 per cent mucin in normal human fluid, while Cajori and Pemberton (14) report a mucin content of 0.42 per cent in fluid from a patient with generalized edema. That the viscosity of synovial fluid is due to the presence of mucin is shown by the fact that the viscosity approaches that of water after removal of the mucin. Comparison of the differences in viscosity and mucin in normal synovial fluids from various animals suggests that the viscosity is related to the degree of polymerization of mucin as well as to the concentration.

Normal human synovial fluid does not clot. This is due presumably to the absence of fibrinogen. No fibrinogen was found by precipitation experiments with 1.1 M phosphate solution at pH 6.5.

The distribution of nonprotein nitrogen between fluid and plasma is approximately the same as that found in cattle fluid (1), in horse fluid (20), and in other fluids shown to have the composition of dialysates of blood plasma (21, 22, 23). The average distribution ratio is 0.91, and many individual cases show an equal concen-

TABLE I

Chemical composition of normal human synovial fluid

	Amount	Relative viscosity	Total solids	Specific gravity	pH	Total protein (exclusive of mucin)		Albumin	Globulin	Mucin
						Fluid	Serum			
	cc.		*grams per 100 grams*			*grams per 100 cc.*		*grams per 100 cc.*	*grams per 100 cc.*	*grams per 100 cc.*
Average *	1.1	150	3.41		7.38	1.72	6.79	1.02	0.05	0.85
Maximum	3.5	403	4.83		7.39	2.13	7.26			1.10
Minimum	0.13	51	2.40		7.36	1.31	6.31			0.55
Number of fluids ‡	46	20	8		2	10	2	1	1	5
Average †	8.0	53	2.23	1.010	7.40	0.63	5.77	0.67	0.17	0.50
Maximum	40.0	174	3.43	1.012	7.45	1.78	7.08	1.45	0.33	1.18
Minimum	0.25	6	1.45	1.008	7.29	0.12	4.44	0.12	0	0.06
Number of fluids ‡	78	7	19	7	4	60	24	6	6	48

* Fluids obtained postmortem from patients without edema.
† Fluids obtained postmortem from patients with varying degrees of edema.
‡ Represents the number of fluids from which the averages were obtained.

tration in plasma and fluid, indicating that the tissue between fluid and plasma in humans is readily permeable to nonprotein nitrogen.

The distribution ratios for sugar show more variation, but the average is 1.12, and many cases show a ratio of 1.00. The variations and the high average ratio are explicable by the fact that the blood sugar was changing rapidly before death and the fluid was not in equilibrium.

Study of the distribution of electrolytes between fluid and plasma in humans has been limited because of the small amount of fluid available. Such determinations as we have made represent fluid from patients with edema (see Table II).

TABLE II

Distribution ratios between serum and synovial fluid

	$\frac{NPN_f}{NPN_s}$	$\frac{Sugar_f}{Sugar_s}$	$\frac{Cl_s}{Cl_f}$	$\frac{\sqrt{Ca_f}}{\sqrt{Ca_s}}$
Average	0.91	1.12	0.98	0.87
Maximum	1.11	2.06	1.00	0.90
Minimum	0.66	0.65	0.91	0.84
Number of fluids*	25	22	15	4

* Represents the number of fluids from which the averages were obtained.

The results, however, are applicable to normal human synovial fluid in general, since membrane equilibrium, if present, would be maintained despite the increased volume of fluid. The two substances (Cl and Ca) which have been studied show distributions similar to those found in cattle fluid and other body fluids having the composition of plasma dialysates. The average distribution ratio of chloride between plasma and human fluid is identical with that for cattle fluid (1). The theoretical Donnan ratio for the two systems is the same. The average ratio $\sqrt{\frac{Ca_f}{Ca_s}}$ also is essentially the same as that for cattle fluid and indicates that part of the calcium is held in the serum presumably bound to protein.

DISCUSSION

Thus, the distribution of non-electrolytes and electrolytes between plasma and normal human synovial fluid is in accord with the findings in normal bovine synovial fluid and indicates that normal human synovial fluid is a dialysate of blood plasma, containing albumin, globulin and mucin.

The presence of serum proteins in synovial fluid can be explained presumably on the basis of slight capillary permeability. Albumin and globulin are found in varying amounts in other body fluids which have been shown to have the composition of simple dialysates of blood plasma (lymph, edema, pleural and ascitic fluids) (21, 22, 23). The high albumin-globulin ratio in normal human fluid indicates a greater permeability to albumin than to globulin.

The presence of mucin in no way invalidates the above theory. The nature of the synovial membrane and the mechanism of formation of mucin have long been discussed. The consensus

of opinion at present is that the joint cavity is a large tissue space lined by somewhat modified connective tissue and not by a true membrane (see review of subject, reference number 24). According to this theory, synovial fluid is the matrix of the connective tissue and the mucin corresponds to the mucoid constituent of other connective tissues. Thus it is generally accepted that mucin is formed by the cells of the synovial tissues, but this process is not secretion as usually defined. Extraction from the subcutaneous tissue of rabbits and the tissue lining the astragalotibial joints of cattle of a substance similar to synovial fluid mucin, as shown by its physical properties and by enzymatic studies (25), confirms the suggestion that mucin is formed by the connective tissue cells surrounding the joint. Its entrance into the joint is made possible by diffusion of plasma water from the underlying blood vessels through the synovial tissues.

The results of the present investigation confirm those of normal cattle fluid studies and give experimental evidence for the theory that normal human synovial fluid is a dialysate of plasma containing albumin, globulin and mucin.

The above characterization of normal human synovial fluid affords a basis of comparison for the findings in pathological synovial fluids and thereby increases the value of joint aspirations. Analysis of pathological fluids from various joint diseases will be presented in a later publication.

SUMMARY

Normal human synovial fluid is a relatively cell-poor, clear, pale yellow, viscous liquid. It has an average nucleated cell count of 63 per cu.mm. The average differential cell count is: 63 per cent mononuclear phagocytes, 24.6 per cent lymphocytes, 6.5 per cent polymorphonuclear leukocytes, 4.3 per cent synovial cells and 2.2 per cent unidentified cells. The relative viscosity is 150 at 25° C. The pH is 7.39.

The average total albumin and globulin content is 1.72 grams per 100 cc.; in one normal fluid the albumin and globulin fractions were 1.02 grams and 0.05 gram, respectively. The average content of mucin is 0.85 gram per 100 cc. Fibrinogen is absent.

The distribution of non-electrolytes and electrolytes between serum and fluid is in accord with the concept that synovial fluid is a dialysate of blood plasma containing albumin, globulin and mucin.

The presence of mucin distinguishes synovial fluid and similar connective tissue fluids from other body fluids that are dialysates of plasma.

BIBLIOGRAPHY

1. Ropes, M. W., Bennett, G. A., and Bauer, W., The origin and nature of normal synovial fluid. J. Clin. Invest., 1939, **18**, 351.
2. Butler, A. M., and Montgomery, H., The solubility of the plasma proteins. I. Dependence on salt and plasma concentrations in concentrated solutions of potassium phosphate. J. Biol. Chem., 1932, **99**, 173.
3. Coggeshall, H. C., Warren, C. F., and Bauer, W., The cytology of normal human synovial fluid. Anat. Rec., 1940, **77**, 129.
4. Horiye, K., Über die menschliche Synovia. Virch. Arch. f. path. Anat., 1924, **251**, 649.
5. Fisher, A. G. T., Chronic (Non-Tuberculous) Arthritis; Pathology and Principles of Modern Treatment. Macmillan Company, New York, 1929.
6. Seeliger, P., Ein Beitrag zur pathologischen Physiologie der Gelenke unter Berücksichtigung der Gelenkmausbildung. Arch. f. klin. Chir., 1926, **142**, 606.
7. Boots, R. H., and Cullen, G. E., The hydrogen-ion concentration of joint exudates in rheumatic fever and other forms of arthritis. J. Exper. Med., 1922, **36**, 405.
8. Pescatori, F., La fisiopatologia del cavo articolare in rapporto al componente sinoviale. Chir. d. org. di Movimento, 1930, **14**, 451.
9. Bauer, W., Bennett, G. A., Marble, A., and Claflin, D., Observations on the normal synovial fluid of cattle. I. The cellular constituents and nitrogen content. J. Exper. Med., 1930, **52**, 835.
10. Warren, C. F., Bennett, G. A., and Bauer, W., The significance of the cellular variations occurring in normal synovial fluid. Am. J. Path., 1935, **11**, 953.
11. Labor, M., and von Balogh, E., Zytologische und Serologische Untersuchungen der Synovia im Besonderen bei Akuten Gelenksentzündungen. Wien. klin. Wchnschr., 1919, **32**, 535.
12. McEwen, C., Cytologic studies on rheumatic fever. II. Cells of rheumatic exudates. J. Clin. Invest., 1935, **14**, 190.
13. Kling, D. H., Synovial cells in joint effusions. J. Bone and Joint Surg., 1930, **12**, 867.
14. Cajori, F. A., and Pemberton, R., The chemical composition of synovial fluid in cases of joint effusion. J. Biol. Chem., 1928, **76**, 471.
15. Bennett, G. A., and Shaffer, M. F., The passage of proteins from the vascular system into joints and

certain other body cavities. J. Exper. Med., 1939, 70, 277.

16. Field, M. E., Leigh, O. C., Jr., Heim, J. W., and Drinker, C. K., The protein content and osmotic pressure of blood serum and lymph from various sources in the dog. Am. J. Physiol., 1934, 110, 174.
17. Goettsch, E., and Kendall, F. E., Analysis of albumin and globulin in biological fluids by the quantitative precipitin method. J. Biol. Chem., 1935, 109, 221.
18. Weech, A. A., Goettsch, E., and Reeves, E. B., The proteins of blood and subcutaneous lymph in dogs. J. Clin. Invest., 1933, 12, 1021.
19. Wells, H. S., The concentration and osmotic pressure of the proteins in blood serum and in lymph from the lacteals of dogs. Am. J. Physiol., 1932, 101, 421.
20. Hare, T., and Cohen, H., The chemical estimation of the synovial fluid and blood-serum of horses affected with chronic arthritis. Proc. Roy. Soc. Med., 1929, 22, 1121.
21. Heim, J. W., On the chemical composition of lymph from subcutaneous vessels. Am. J. Physiol., 1933, 103, 553.
22. Arnold, R. M., and Mendel, L. B., Interrelationships between the chemical composition of the blood and the lymph of the dog. J. Biol. Chem., 1927, 72, 189.
23. Gilligan, D. R., Volk, M. C., and Blumgart, H. L., Observations on the chemical and physical relation between blood serum and body fluids. I. The nature of edema fluids and evidence regarding the mechanism of edema formation. J. Clin. Invest., 1934, 13, 365.
24. Bauer, W., Ropes, M. W., and Waine, H., The physiology of articular structures. Physiol. Rev., 1940, 20, 272.
25. Robertson, W. v. B., Ropes, M. W., and Bauer, W., Mucinase: A bacterial enzyme which hydrolyzes synovial fluid mucin and other mucins. J. Biol. Chem., 1940, 133, 261.